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Review

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ABSTRACT

Biochemical recurrence after primary treatment in prostate cancer is not uncommon. A rising serum prostate-specific antigen level represents a first sign of disease relapse. At this time of low disease burden, imaging and particularly magnetic resonance imaging and positron emission tomography/computed tomography (PET/CT) are essential to determine the localization of the recurrence, which may be local, in lymph nodes, and/or metastatic. Imaging results allow best determine modalities of salvage treatment, which can be local by using radiotherapy or other focal treatments or systemic using hormonotherapy. Current evidence suggests that multiparametric magnetic resonance imaging, PET/CT with prostate specific membrane antigen and lympho-magnetic resonance imaging are effective and complementary to detect local recurrences and distant metastases.

1. Introduction

Prostate cancer (PCa) is the most common cancer in men, with more than 50 thousand new cases per year in France, ranking the fifth death cause among two sexes [1]. In patients treated by local curative therapies for PCa, the measurement of prostate-specific antigen (PSA) is a key component of the follow-up strategy because a rising serum PSA level is often the first sign of relapse. This so-called biochemical recurrence (BCR) almost always precedes clinical recurrence [2,3]. Its rate varies from 20 to 50%, depending of the initial treatment and stage of the disease [4,5]. It is a quite challenging issue for physicians because on the one hand not all BCR have the same clinical value as they have different thresholds regarding to previous treatments; on the other hand, a measurable PSA may not necessarily lead to clinically apparent metastatic disease [6]. Local and regional recurrence after radical prostatectomy (RP) or after radiotherapy (RT) can be treated using salvage treatment (RT, focal therapy). In patients with PCa, imaging is a pivotal tool for discovering the site(s) of recurrence and the extent of the disease. Proper identification is crucial for subsequent treatment decisions because, curative local treatments can still be feasible for local recurrence or locoregional lymph node (LN) metastasis, while patient with distant metastasis should have palliative treatment or stereotactic body radiation therapy, which may induce a long-lasting complete remission [7].

Metabolic imaging is taking an increasingly prominent role in localizing recurrence, especially with the high reliability of prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/ computed tomography (CT). PET/CT can show both local, LN, and bone recurrence, whereas the all-in-one magnetic resonance imaging (MRI) is an imaging technique that is not listed in the nomenclature in France, which is a disadvantage compared to PET/CT. Moreover, whole body (WB) MRI to detect bone metastases is a combination of T1-weighted (T1W) acquisition and WB diffusion-weighted imaging (DWI), whose long acquisition time could explain limited use in clinical practice. Nevertheless, the three-dimensional (3D) T1W acquisition, using either a fast spin-echo or a much shorter gradient echo (GE) Dixon sequence, made possible an examination time of 20 min.

Multiparametric (mp) MRI definitely continues to play a role in the detection of local recurrence, but conventional mpMRI has limitations in the detection of LN metastases. An improvement has come

Abbreviations: 3D, Three-dimensional; ADC, Apparent diffusion coefficient; AI, Artificial intelligence; BCR, Biochemical recurrence; CT, Computed tomography; DCE, Dynamic contrast-enhanced; DWI, Diffusion-weighted imaging; EAU, European Association of Urology; EB, External beam; FACBC, Fluciclovine; GE, Gradient-echo; LN, Lymph node; Mp, Multiparametric; MRI, Magnetic resonance imaging; PCa, Prostate cancer; PET, Positron emission tomography; PSA, Prostate-specific antigen; PSMA, Prostate-specific membrane antigen; RP, Radical prostatectomy; RT, Radiotherapy; T1W, T1-weighted; T2W, T2-weighted; WB, Whole-body

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from a combination of DWI and morphological imaging with a high spatial resolution 3D T2-weighted (T2W) acquisition [8]. Moreover, the use of lympho-MRI, may improve substantially the diagnostic accuracy for LN metastasis. Lympho-MRI is currently being reevaluated at the University of Nijmegen and is undergoing a phase 3 evaluation. Lympho-MRI uses highly lymphotropic superparamagnetic nanoparticles, which gain access to lymph nodes by means of interstitial-lymphatic fluid transport and allows MRI to reveal small nodal metastases [9]. MRI will probably be complementary to PET-CT, with persistent, but selected indications. However, timing and treatment modality for PSA-only recurrences remain a matter of controversy based on limited evidence [6].

The purpose of this review article was to provide an overview of the current practice of diagnosis of BCR after RP and RT, including the latest advancements and newest imaging techniques.

2. Clinical background

2.1. Definition of BCR

After RP, serum PSA level must be undetectable within six weeks when there is no residual cancer [10]. The lowest PSA value obtained after treatment is called "nadir"; follow-up is mainly based on the PSA dosage. When the PSA increases and reaches a threshold of 0.2 ng/mL, twice consecutively after surgery, the BCR is confirmed [11]. Some authors suggested that 0.4 ng/mL could be a better cut-point because it shows the strongest association with subsequent systemic progression [12].

After external beam (EB) RT, the Phoenix criteria defines the threshold for BCR at a PSA value ≥ Nadir + 2 ng/mL [13,14]. Among several proposed definitions, this definition was chosen because it allowed the best compromise of sensitivity and specificity, taking into account possible rebound phenomena [15]. It predicts clinical recurrences with an accuracy of about 80% [13].

2.2. Predictors of local and distant recurrences

After RP, the pattern of treatment failure is predominantly local (60%) with a relatively low incidence of metastatic failure [16–18]. Some clinico-pathological features and characteristics of PSA recurrence represent important variables when trying to distinguish between local and distant recurrence.

Seminal vesicle involvement or pelvic LN invasion at the time of surgery, a Gleason score (GS) > 7 [19] or negative margin status after surgery [20] seem to be associated with distant recurrences. Similarly, BCR occurring within six months of RP is a strong indicator of metastases [21]. On the contrary, an interval >1–2 years between BCR and RP suggests that the relapse is more likely to be local [17,19,22]. More recently some serum biomarkers such as pigment epithelium-derived factor can improve the prediction of BCR and could be integrated into prediction models for BCR following RP [23].

After EBRT, factors that predict a high risk of metastases and PCa-specific mortality are similar to those after RP and include a PSA doubling time <3 months, clinical stage cT3b–T4, biopsy Gleason score 8–10, or BCR within three years of RT [6, 24-27]. An uncertainty for higher risk also exists, when PSA doubling time is between 3 and 15 months [28]. These characteristics were summarized in Tables 1 and 2.

Nevertheless, these indirect criteria in favor of local and distant recurrence were developed before current imaging was available, making them probably less important. Moreover, all three types of recurrence are searched in any patient presenting with BCR.

Table 1
Predictors of local and distant recurrences after radical prostatectomy.

Local recurrences	Distant recurrences
Gleason Score ≤ 7	Gleason Score > 7
Without seminal vesicle involvement	Seminal vesicle involvement
Without pelvic LN invasion	Pelvic LN invasion
Positive margin status after surgery	Negative margin status after surgery
BCR occurring remotely from primitive treatment	BCR occurring rapidly after primitive treatment (within 6 months)
Velocity of PSA < 0.5 ng/mL/month	Velocity of PSA > 0.75 ng/mL/year
PSAdt > 6 months	PSAdt < 6 months

LN: Lymph node; BCR: Biochemical recurrence; PSA: Prostate-specific antigen; dt: Doubling time.

Table 2
Predictors of local and distant recurrences after radiotherapy.

Local recurrence	Distant recurrence
Gleason Score ≤ 7	Gleason Score > 7
Without seminal vesicle involvement	Seminal vesicle involvement
Without pelvic LN invasion	Pelvic LN invasion
BCR occurring remotely from primitive treatment	BCR occurring rapidly after primitive treatment (within 3 years)
PSAdt > 3 months	PSAdt < 3 months

LN: Lymph node; BCR: Biochemical recurrence; PSA: Prostate-specific antigen; dt: Doubling time.

2.3. Management of BCR

The options for treatment of recurrence after RP are, according to the European Association of Urology (EAU), RT at least to the prostatic fossa, continuous or intermittent hormonal therapy, or simple monitoring [6]. Because many BCR are due to a local relapse, salvage RT may have a curative role [29]. Despite the definition of the BCR, it becomes a current practice to wait until serum PSA level reaches 0.5 ng/mL, in order to detect a target in the prostatic bed so then to increase the radiation dose locally [6]. Usually, the dose delivered is around 66 Gy, but could be increased when local relapse is detected by imaging.

After EBRT, local salvage treatment should be considered only for selected patients. Salvage RP is most likely to achieve local control [30]. Other salvage options are cryoablation, high-intensity focused ultrasound, stereotaxic RT and brachytherapy. Salvage cryoablation of locally recurrent PCa after curative treatment is feasible and safe when the half prostate is treated. It could delay initiation of androgen deprivation therapy in these patients [31]. Because of a lack of quality data, there is no recommendation regarding the indications for specific salvage treatments [6]. In patients with oligo-metastases, ablative treatments by stereotactic body radiation therapy are effective and delay androgen deprivation therapy, leading to better patients' prognosis [32].

2.4. mpMRI and PET imaging

After RP, the main role of mpMRI is the detection of local recurrence, which is an important issue since the pattern of treatment failure is predominantly local. Identification of lesions in the prostatectomy bed could translate to higher radiation doses realizing a “radiation boost”, this recommendation exists mainly in the community of radiotherapists, which are in favor of prostate bed MRI [33]. However its indication in this setting has not been validated yet [6]. mpMRI is a well validated tool for patients without distant metastases and fit for local salvage therapy [6]. So far, EAU recommended mpMRI as the best technique to assess local recurrence and guide

targeted biopsies for patient who are considered for local salvage therapy [6].

The protocol of mpMRI is the same as that performed for tumor detection, compliant with European Society of Uro-Radiology guidelines with T1-weighted (T1W), T2-weighted (T2W), DW (with high *b* values > 1400 s/mm^2) and dynamic contrast-enhanced (DCE) imaging sequences [34]. T2W images should be acquired in three orthogonal planes (axial, coronal, and sagittal) including the vesicourethral anastomosis, the residual seminal vesicles, when present, and the complete posterior wall of the bladder, as these are the primary sites of relapse [34]. Acquisition of at least one pulse sequence with a large field of view (either T1W or DWI, with *b* values of 50/100 and 900/1000 s/mm^2) is also advised to assess for the presence of large lymph nodes and bone marrow abnormalities. Also, the presumption of malignant lesion increases with the number of positive sequences [34].

The main goal of PET imaging is to identify patients with metastatic disease that would not benefit from local treatment. The interpretation is based on the search of the uptake foci of radiotracer, in light of proper identification of physiological uptake.

Many PET tracers are available, including choline-based radiotracers, fluciclovine (FACBC) and PSMA. ^{18}F Fluorodeoxyglucose and ^{18}F sodium fluoride PET are two others widely used PET tracers but because of very limited clinical utility in PCa they will not be discussed. Choline is a component of cell membrane phospholipids, which is an interesting biomarker for cell proliferation imaging. A change in the metabolism of choline has been reported in many neoplasia including PCa, reflecting an increase in its availability to proliferating cancer cells, due to an increase intracellular transport of choline and the activity of the enzyme choline kinase [35]. It can be labeled with ^{18}F or ^{11}C. FACBC targets the L-type amino acid transporter type 1 and ACST2 transmembrane transporters, both of them being overexpressed in PCa cells [36]. PSMA is a well-recognized biological target in PCa. It plays an important role in glutamatergic neurotransmission and folate absorption, and is also involved in prostate carcinogenesis and progression [37]. Horoszewicz et al. identified the PSMA-positive PCa cell line LNCaP [38] and ^{111}In-labeled 7E11-C5 became the first FDA-approved imaging agent for PCa known as ProstaScint® [39]. Then ProstaScint® failed to gain a wide acceptance because of the intrinsic inferiority of single photon emission computed tomography compared to PET. Molecular imaging PSMA ligands for PET imaging have been developed such as ^{68}Ga PSMA-11, ^{18}F PSMA-1007, ^{18}F DCFPyl, and ^{18}F DCFBC, which all bind irreversibly to the extracellular component of PSMA, making them highly specific tracers in PCa [6].

3.2. MRI features and role of MRI in different clinical settings

3.2.1. Local recurrence

3.2.1.1. Local recurrence after radical prostatectomy. Post RP MRI findings include descent of the bladder, which is anastomosed to extraprostatic distal urethra. Tissues adjacent to the vesico-urethral anastomosis harbor low signal on T2W MRI. The vas deferens/ and seminal vesicle which are supposed to be removed may be left in place.

Vesico-urethral anastomosis is the most common site of local recurrence after RP, but recurrent lesions can occur anywhere in the prostatectomy bed including the retro-vesical space, the bladder wall, near the seminal vesicles bed, or adjacent to the vas deferent.

Local recurrence usually presents as a nodular, semi circumferential to ill-defined soft-tissue lesion of intermediate signal intensity on T2W images with associated restricted diffusion and rapid, early enhancement on DCE imaging (Fig 2). The signal intensity of recurrence on T2W images is not the same than that of the initial tumor. It exhibits hyperintensity, compared to the marked hyposignal of the anastomotic fibrosis. Also, the presumption of malignant lesion increases with the number of positive sequences [34].

3.2.1.2. Local recurrence after external beam radiotherapy. EBRT induces changes in prostate including gland shrinkage, loss of normal anatomy, and decreased contrast between PCa and normal prostatic tissues on T2W imaging due to glandular atrophy and fibrosis. Thus, recurrence can be difficult to detect on T2W images and use functional sequences is essential.

Local recurrence is most common in the gland at the site of the original primary tumor. mPMRI performed remarkably well in detecting recurrent PCa after EBRT. It appears as a mass-like abnormality slightly hypointense on T2W images compared to treated prostatic tissue. On DW imaging, local recurrence displays focal hyperintensity on high *b* values (> 1400 s/s/mm$^{2)}$ images corresponding to a dark area on the apparent diffusion coefficient (ADC) map, which may or may not correspond to a nodular area visualized on T2W images (Fig 3). On DCE imaging, local recurrence can present as an enhancing focal lesion that “shines” against the background of non-enhancing or only minimally and slowly enhancing surrounding tissue [34]. It is now commonly admitted that mpMRI is a reliable tool for lesion detection and follow-up in this setting, providing essentially qualitative data and possibly quantitative data (Fig 3) [40].

In the post RP setting, the performance of MRI remains modest. In a series of 88 men who underwent MRI for a clinically undetectable post-RP BCR, Liauw et al., identified a threshold of 0.3 ng/mL for PSA; recurrence was seen in 37% of men with PSA >0.3 ng/mL and in only 13% of men with PSA ≤0.3 ng/mL (P<0.01) [33].. However, these values remain too low to be used in clinical practice. Nevertheless, MRI still has a place for patients with serum PSA levels between 0.1 and 0.5 ng/mL. It is established that MRI performs better than choline PET/CT, but evidence is lacking on the non-inferiority on MRI compared to PSMA PET-CT for PSA values < 0.5 ng/mL. Above this threshold, it is likely that PSMA and MRI perform equally [6]. In practice, MRI of the prostate bed is generally performed, as radiotherapists require MRI of the prostate bed to look for a lesion and a better post-surgical pelvic anatomy evaluation. Even though this practice does not follow exactly the EAU recommendation (Table 3).

In the post RT setting, mpMRI is a well validated tool. The sensitivity and specificity of the combination of T2W and DWI are, respectively, 94% and 75%, for the detection of recurrences > 0.4 cm^2 [41]. Donati et al. and Akin et al., found that DWI and DCE imaging allowed accurately identify local recurrence in the irradiated prostate [42,43]. Although usually considered part of the prostate mpMRI protocol, the incremental value of DCE MR imaging remains uncertain. Alonzo et al. studied 45 patients treated only by EBRT and found no differences between T2W+DWI+DCE and T2W+DWI for four readers at 3T (P = 0.34–0.69) [44]. Nevertheless, the authors did not indicate whether tumor volumes were identical on both DWI and DCE. Since the target volume is important before considering focal ablation in order to cover the entire area to be treated, DCE should be used in this setting. Luzurier et al. found that T2W+DWI+DCE significantly improved the sensitivity for junior readers and inter-reader agreement between two junior and two senior readers [45]. But the addition of DCE imaging did not significantly improve the accuracy in recurrent PCa detection after radiotherapy, whatever the level of experience of the readers [46]. However, because DWI is prone to susceptibility artifacts and distortion, DCE imaging can be helpful in patient with incomplete rectal preparation or hip prosthesis, revealing an intense enhancement of the recurrence compared with the fibrous adjacent tissue [47].

3.2.2. Lymph nodes involvement

Both after RP and RT, no studies have identified morphologic characteristics that could help discriminate between normal and metastatic LN. On the opposite, at the initial staging: LN is generally

Table 3
Summary and recommendation of imaging for BCR after PR and RT (adapted from EAU 2021 guideline).

BCR after PR		**BCR after RT**	
PSA level < 1 ng/mL	PSA level > 1 ng/mL and PSMA PET/CT not available	Regardless of PSA level	
Perform PSMA PET/CT No imaging if PSMA PET/CT not available	Perform FACBC or choline PET/CT	For patients fit for local salvage therapy	For patients fit for curative salvage treatment
		If PET/CT negative: perform prostate mpMRI to localize abnormal areas and guide biopsies If PET/CT positive: do not perform mpMRI*	Perform PSMA PET/CT If PSMA not available: perform FACBC or choline PET/CT
Strength rating: weak	Strength rating: weak	Strength rating: weak	Strength rating: strong

BCR: Biochemical recurrence; PR: Radical prostatectomy; RT: Radiotherapy; EAU: European Association of Urology; PET/CT: Positron emission tomography/computed tomography; PSA: Prostate-specific antigen; PSMA: Prostate-specific membrane antigen; FACBC: Fluciclovine; mpMRI: Multiparametric magnetic resonance imaging.
* In practice, even when PET/CT is positive, mpMRI is usually performed to guide biopsies.

considered abnormal if the short axis is ≥1 cm or if the LN is morphologically abnormal regardless of size (*i.e.*, rounded, loss of fatty hilum, spiculated margins, asymmetric cortical thickening, heterogeneous, low signal intensity on T2W imaging). Nevertheless, these criteria are not very reliable since metastatic LN may be normal sized and non-metastatic LN may be enlarged due to reactive hyperplasia. Thus, in the recurrence setting, metastatic LN are difficult to characterize based on morphologic characteristics alone. Moreover, after pelvic radiation, metastatic LN could be located above the radiation field (*i.e.*, at the aortic bifurcation or even periaortic).

Currently, there are no data regarding the performances of MRI in the BCR setting. Nevertheless, it is a compelling tool in the setting of initial staging. MRI, which used only morphologic criteria for LN assessment, has limitations for the detection of lymph nodes involvement, as in PCa more than 60% of LN metastases are present in normal-sized LNs (<8 mm) [48]. Thoeny et al. has highlighted the accuracy of a combination of DWI and T2W to detect LN metastasis of PCa in normal sized LN, with 64–79% sensitivity and 79–85% specificity at a per-patient level [8]. In the study by Schilham et al. lympho-MRI using ultrasmall superparamagnetic iron oxide detected significantly more suspicious LNs per patient compared to ^{68}Ga PSMA PET-CT, and the difference was especially found for micrometastasis [48]. However, it is important to note that in this latter study no histopathological confirmation was made to confirm the actual status of LNs detected and presumed to be metastatic, which is a serious limitation [48].

3.2.3. Bone metastasis

MRI is a well-established technique for the characterization of bone metastasis. Bone metastases from PCa mainly present as hypointense lesions on T1W images compared to muscle, and hyperintense on T2W images. They are hyperintense on DWI with a low ADC value, due to water restriction.

WB MRI has excellent performance to assess bone metastasis [49, 50]. Barchetti et al. evaluated the performance of unenhanced WB MRI for the detection of lesions in the setting of BCR in 152 patients using choline PET as the standard of reference [49] and they found WB MRI allowed the diagnosis of bone metastases with 99% sensitivity, 98% specificity, 98% positive predictive value, 96% negative predictive value, and 98% accuracy [49]. Similarly, Wieder et al. reported a sensitivity of 88% for WB MRI as in the detection of metastatic disease following BCR in 50 patients with PCa, in comparison to ^{11}C-choline PET, which had a sensitivity of 94% [50]. In another study by Eiber et al., the authors concluded that WB MRI is technically robust in patients with recurrent PCa [51]. In 30 consecutive patients with PCa who were considered at high risk for metastases, including those in BCR setting, Pasoglou et al. proposed a protocol requiring an acquisition time of only 35 min [52]. This protocol includes a combination of 3D T1W sequence and WB DWI covering four segments from the base of the skull to the proximal part of the femurs [52]. Moreover, a more recent study showed that a 3D GE T1W sequence, at 3T, required only 1 min and 20 s to obtain a WB MRI examination in less than 20 min, including the WB DWI sequence [53]. This protocol could improve the acceptance of WB MRI in the radiologic community.

Ideally, the N and M evaluation should be performed with an acquisition time that does not exceed that of a usual prostate MRI examination. Recent data reported that it was probably unnecessary to perform all three available sequences (T1, STIR and diffusion) and two sequences seem sufficient. As DWI is also used for LN evaluation, is the use of 3D-T1 (Dixon GE) + DWI should be preferred to that of 3D-T1 (Dixon GE) + STIR [54].

3.3. Role of PET in different clinical settings

3.3.1. Choline-based radiotracers PET imaging

Compared to ^{99}mTc-labelled diphosphonates bone scan, choline PET/CT may detect more bone metastases [55]. Detection of LNs metastases remains limited by the relatively poor sensitivity (49%), also for its false positive rate, as highlighted this meta-analysis [56].

^{11}C Choline PET/CT sensitivity is strongly influenced by serum PSA level and kinetics. It drops to sub-optimal values in patients with a low PSA [57]. Indeed, its detection rates are only 5–24% when the PSA level is < 1 ng/mL, but rises to 67–100% when the PSA level is > 5 ng/mL [6, 56]. For detection of local recurrence, ^{11}C Choline PET/CT is less sensitive than mpMRI when the PSA level is < 1 ng/mL [57]. Despite its limitations, ^{11}C Choline PET/CT may change medical management up to 47% of patients with BCR after primary treatment [58]. Choline PET/CT should only be recommended in BCR patients if the PSMA PET is not available [6] and the PSA cut-off level for indication of choline PET/CT analysis is proposed between 1 and 2 ng/mL [59]. In the only study exploring the role of Choline PET/CT in the setting of post-RT BCR with a low PSA level, Rybalov et al. found a detection rate of 88% for the local recurrence using ^{11}C choline PET in 42 patients compared to a composite reference after local salvage treatment [60].

3.3.2. FACBC PET imaging

One advantage of ^{18}F FACBC is a limited urinary excretion, which facilitates the evaluation of local recurrent disease [61]. In a recent multicenter trial evaluating 596 patients with BCR in a mixed population (33.3% after RP, 59.5% after RT ± RP, 7.1% others), ^{18}F FACBC PET/CT had an overall detection rate of 68% and a sensitivity of 62.7% [62]. The detection rate reached 41% in the group of patients with PSA < 0.79 ng/mL [62]. A meta-analysis including six studies and 251 patients showed that the pooled sensitivity and specificity for the diagnosis of PCa recurrence on a per-patient analysis was 87% (95% CI: 80–92) and 66% (95% CI: 56–75%), respectively [63]. As for choline

PET/CT, ^{18}F FACBC PET/CT sensitivity is dependent on the PSA level, with a sensitivity < 50% when serum PSA level is < 1 ng/mL [6]. As a result, ^{18}F FACBC PET/CT should be recommended in patients with BCR only when PSMA PET is not available [6]. To date, there are no studies that consider or suggest the role of FACBC PET imaging in PCa in the setting of post-RT BCR.

3.3.3. PSMA PET-CT imaging

PSMA PET/CT-positivity rates depends strongly on serum PSA level. In a recent meta-analysis including 43 studies with 5113 patients, Tan et al. analyzed the performance of PSMA PET/CT for the detection of BCR stratified by PSA level [64]. The pooled detection rate was 70.2% for the entire cohort, ranging from 44.9% for a PSA level of less than 0.5 ng/mL to 93.9% for a PSA level of at least 2 ng/mL on stratified subgroup analysis [64]. All the studies showed a maximal detection rate of 90% at a PSA level ≥ 2 ng/mL, which is consistent with the fact that around 5%–10% of PCas do not overexpress PSMA and are thus PSMA-negative [65].

In a systematic review including 98 studies in PCa patients with BCR, PSMA PET had greater detection rates than any other imaging modality, especially for low PSA values [66]. Indeed, the detection rates ranged from 11.3% to 58.3% at PSA levels <0.2 ng/mL and from 11.0% to 65.0% at PSA levels <0.5 ng/mL, respectively [66].

PSMA PET/CT seems substantially more sensitive than choline PET/CT in detecting PCa recurrence, especially when serum PSA level is < 1 ng/mL [67], and also than FACBC PET/CT, in a small prospective study including 10 patients with BCR [68]. Different authors tried to define an optimal serum PSA threshold value to undergo PSMA PET. For Sanli et al. it was 0.67 ng/mL [69]; Hope et al. suggested 1.5 ng/mL [70]. Farolfi et al. highlighted the potential role of PSMA PET/CT especially for the identification of distant metastases, even at PSA levels < 0.5 ng/mL [71]. Like in the setting of post-RP BCR, PSMA PET displays excellent performance.

In a retrospective study including 264 patients, Raveenthiran et al. found an overall detection rate of 86.3% using ^{68}Ga-PSMA in patients with a median serum PSA level of 3.60 ng/mL [72]. In the study lead by Einspieler et al., 118 patients were included and 90.7% of them showed pathologic findings indicative for tumor recurrence on ^{68}Ga PSMA PET/CT [73]. The detection rates were 81.8% (36/44), 95.3% (41/43), and 96.8% (30/31) for serum PSA level of 2 to <5, 5 to <10, and ≥10 ng/mL [73]. In a recent study by Jansen et al. PSMA PET/CT detected recurrence in 63 patients not meeting the Phoenix criteria [74]. In 53 of them (84.1%), PSMA-avid lesions were detected; 21 patients (33.3%) had a local recurrence as a single site of disease and 32 patients (50.8%) had metastatic PCa [74].

In practice, when PET/CT is positive and salvage focal ablation is considered, a targeted biopsy should be performed. Thus, it is contrary to the EAU recommendation shown in the Table 3 as prostate MRI is performed to guide biopsies.

3.4. PET/MRI

PET/MRI combines the functional and molecular information of PET with morphological information of MRI. Choline or PSMA are the two main radiotracers utilized. The advantages of PET/MRI over PET/CT include the better anatomical correlation of intraprostatic and bone marrow lesions, both of which being not well assessed using CT. The disadvantages of PET/MRI are its limited availability, and a scanning time significantly longer, about one hour compared to PET/CT.

For choline PET, Eiber et al. performed a prospective comparison of ^{11}C choline PET/MRI and [11C] choline PET/CT in 75 patients (57 RP, 13 ERT, 5 HT) and showed that the local recurrence detection rate of PET/MRI was greater than that of PET/CT, for patients with PSA <2 ng/mL [75]. Regarding PSMA PET, Kranzbuhler et al. highlighted that ^{68}Ga PSMA-11 PET/MRI was a promising tool for 56 PCa patients with early BCR associate with low serum PSA values [76]. Indeed, the detection rate was 60% for patients with PSA between 0.2 and 0.5 ng/mL [76]. Another study Grubmüller et al., in 71 PCa patients with BCR, ^{68}Ga PSMA-11 PET/MRI yielded detection rates of 65% for a

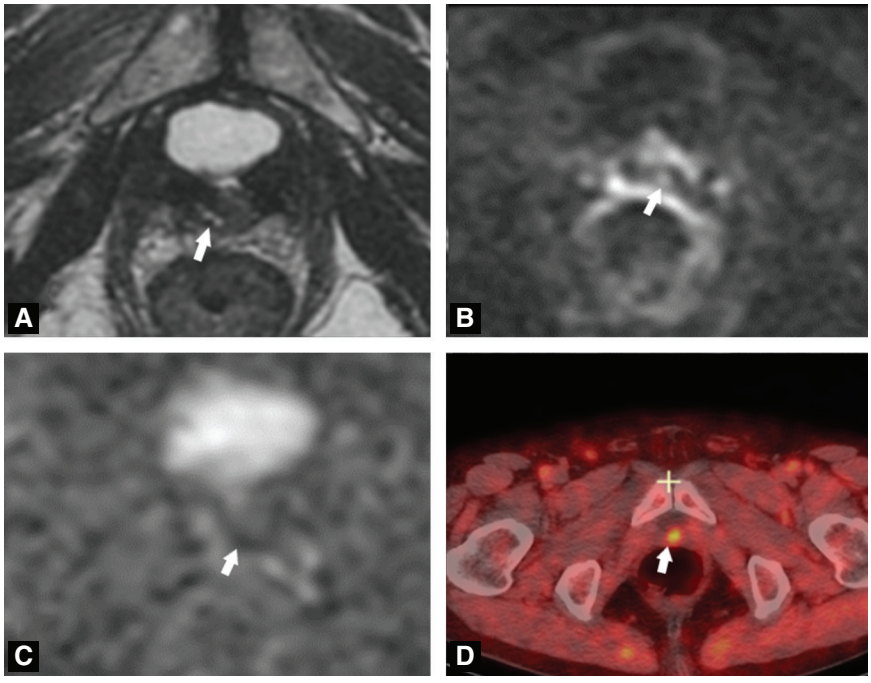

Fig. 1. 78-year-old man with serum prostate-specific antigen = 0.5 ng/mL after radical prostatectomy. Local recurrence after radical prostatectomy was depicted on multiparametric magnetic resonance (MR) imaging and ^{18}F choline positron emission tomography computed tomography (A), T2-weighted MR image in the axial plane shows slightly hyperintense, 6-mm lesion (arrow). (B), Diffusion-weighted MR image in the axial plane shows hyperintense lesion (arrow). (C), Apparent diffusion coefficient map shows lesion with moderate diffusion (arrow). (D), ^{18}F Choline positron emission tomography/computed tomography fused image in the axial plane shows lesion with significant uptake of ^{18}F choline (arrow). All these findings are consistent with local recurrence of prostate cancer in the bladder neck.

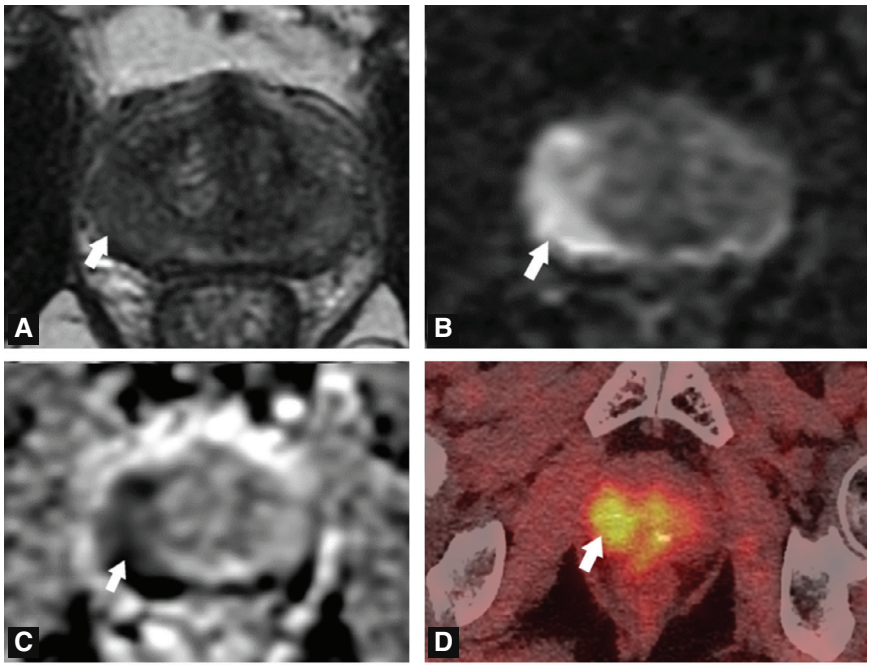

Fig. 2. 71-year-old man with serum prostate-specific antigen = 3 ng/mL after external radiation therapy. Local recurrence after radiotherapy was depicted on multiparametric magnetic resonance imaging and ^{18}F choline positron emission tomography computed tomography. (A), T2-weighted magnetic resonance (MR) image in the axial plane shows hypointense nodular lesion (arrow) in the right peripheral zone. (B), Diffusion-weighted MR image in the axial plane shows hyperintense lesion (arrow). (C), Apparent diffusion coefficient map shows lesion with restricted diffusion (arrow). (D), ^{18}F choline positron emission tomography/computed tomography fused image in the axial plane shows a 20-mm lesion (arrow) in the right peripheral zone suggestive of local recurrence. This lesion demonstrates significant uptake of ^{18}F choline without any distant uptake (neither lymph node nor bone metastasis). Targeted biopsies confirmed prostate cancer recurrence.

serum PSA level value of 0.2 to <0.5 ng/mL, 85.7% for 0.5 to <1 ng/mL, and 85.7% for 1 to <2 ng/mL [77].

The only study which included a significant number of patients in this setting was led by Hope et al. [70]. Indeed, this study enrolled 41 patients with BCR post-RT and 43 patients with BCR post-RP. In patients previously treated with RT, mean serum PSA level was 9.9 ± 14.6 (SD) ng/mL [70]. However, only overall detection rates were reported and were 58.3% for PSA ≤0.2 ng/ml; 61.5% for 0.2 < PSA ≤0.5 ng/mL; 63.6% for 0.5 < PSA ≤1 ng/mL; and 78.3% for 1 < PSA ≤2 ng/mL, respectively [70]. The authors also reported that a major changes in management occurred more frequently for patients previously treated with RT than for those treated with RP [70].

4. Potential value of artificial intelligence

Artificial intelligence (AI) has already become a reality in radiology clinic routine in many indications [78, 79, 80, 81]. The U.S. Centers for Medicare and Medicaid Services officially granted their first-ever reimbursement of a radiology AI algorithm in September 2020, which should open the door to a broader application of AI software in daily practice.

Recent studies have highlighted the potential of AI in PCa imaging [80, 81]. In this regard, Wessels et al. have developed a deep learning approach to predict lymph node metastasis directly from primary tumor histology in PCa [80]. Transin et al. have assessed a computer-aided diagnosis system for characterizing ISUP grade 2 PCa with

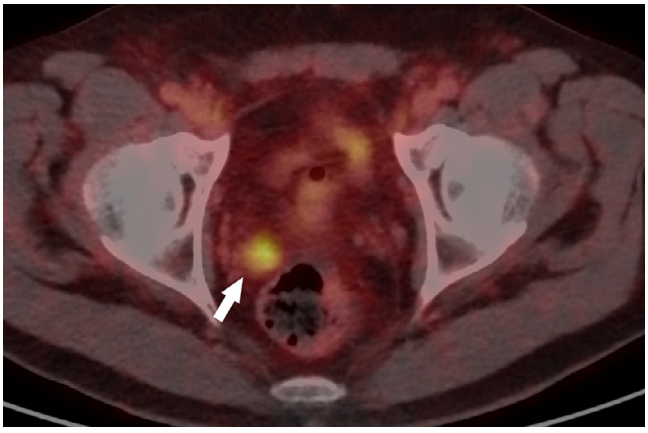

Fig. 3. 63-year-old man with serum prostate-specific antigen = 0.4 ng/mL after radical prostatectomy. Prostate-specific membrane antigen positron emission tomography/computed tomography fused image in the axial plane shows a lesion of 15 × 14 mm (arrow), just above the prostatectomy bed and on the right lateral side of the rectum. The lesion shows substantial uptake of prostate-specific membrane antigen, suggestive of local recurrence. No lymph nodes and no distant metastases were visible.

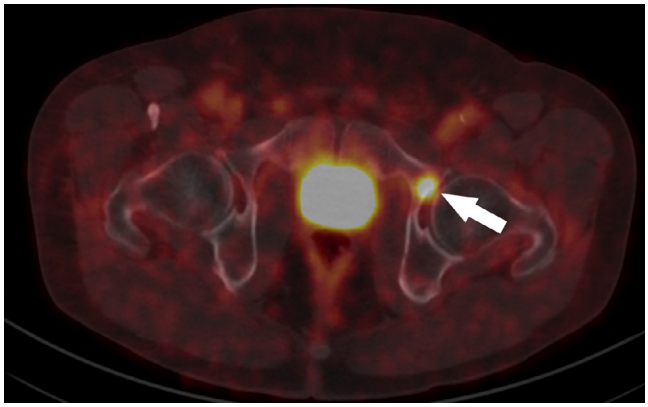

Fig. 4. 65-year-old man with serum prostate-specific antigen = 0.5 ng/mL after radical prostatectomy. Prostate-specific membrane antigen positron emission tomography computed tomography fused image shows lesion (arrow) of the left acetabulum, without osteosclerosis changes, with high uptake of prostate-specific membrane antigen, suggestive of bone metastasis.

mpMRI and found that computer-aided diagnosis system was equivalent to PI-RADSv2 scores for characterizing ISUP grade≥2 cancers [81]. The application of AI in nuclear medicine in the field of PCa has not been described yet but studies are ongoing.

5. Conclusion

Early detection and localization of PCa recurrence is crucial for treatment success and patient survival after RP and EBRT. Knowledge of most appropriate diagnostic imaging strategy, respective diagnostic capabilities of each modality, alone or in combination, is essential to optimize patient management. PET imaging, especially PSMA PET represents a marked advance to detect local recurrence and distant metastases of PCa after RP even in patients with very low serum PSA level (*i.e.*, < 0.5 ng/mL). PET imaging in combination with mpMRI, pending a strict protocol for mpMRI [82], and targeted biopsy are the reference techniques for accessing local recurrences after RT in patient candidates for salvage treatment Fig 1, 4.

Human rights

Not applicable for review articles

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patients.

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