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REVIEW ARTICLE

Imaging biomarkers in prostate cancer: role of PET/CT and MRI

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Abstract Prostate-specific antigen (PSA) is currently the most widely used biomarker of prostate cancer (PCa). PSA suggests the presence of primary tumour and disease relapse after treatment, but it is not able to provide a clear distinction between locoregional and distant disease. Molecular and functional imaging, that are able to provide a detailed and comprehensive overview of PCa extension, are more reliable tools for primary tumour detection and disease extension assessment both in staging and restaging. In the present review we evaluate the role of PET/CT and MRI in the diagnosis, staging and restaging of PCa, and the use of these imaging modalities in prognosis, treatment planning and response assessment. Innovative imaging strategies including new radiotracers and hybrid scanners such as PET/MRI are also discussed.

Keywords Prostate cancer · Biomarker · Imaging · PET/CT · MRI

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Introduction

In clinical practice, multiple biomarkers are generally required in the evaluation of cancer to fully cover screening, diagnosis, prognosis and prediction [1]. In particular, in prostate cancer (PCa) prostate-specific antigen (PSA) was approved by the Food and Drug Administration in 1986 as an adjunctive test to digital rectal examination for the detection of PCa in men older than 50 years, and further studies also demonstrated that the combination of a serum PSA measurement and other clinical findings may improve detection of prostate neoplasm [2, 3]. Recently, the European Association of Urology has suggested PSA determination at age 40 years to provide a baseline value on which the subsequent screening interval may then be based. Specifically, a screening interval of 8 years might be appropriate in men with initial PSA levels ≤1 ng/ml, and in men older than 75 years with a baseline PSA ≤3 ng/ml, because of their very low risk of dying from PCa, further PSA testing seems not to be necessary [4]. Currently, PSA remains the least expensive and most widely used biomarker for screening and treatment monitoring. Despite this, the use of PSA has important limitations. In particular, it is not able to clearly distinguish local from distant disease. Additionally, there is considerable variation in the interpretation of the prognostic role of PSA measurements after treatment. Finally, data are still inconclusive regarding the possible value of PSA levels in predicting survival [5]. In light of this, novel, accurate and cost-effective markers are needed to improve the management of PCa patients in terms of early diagnosis, staging and follow-up.

Pathological staging and grading, as detected by imaging modalities, can be also considered as biomarkers since they can affect PCa prognosis as demonstrated by several nomograms predicting biochemical recurrence and PCa mortality after radical prostatectomy (RP) [6–9]. In particular, molecular imaging and MRI can provide useful information that may

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have a major impact on clinical practice in the management of PCa patients [10].

In the present review we evaluate the role of PET/CT and MRI findings as imaging biomarkers of PCa, addressing their clinical impact on treatment management and prognosis in both staging and restaging phases. An overview of the role of PET/CT and MRI in PCa detection, staging, restaging and treatment guide and response assessment as well as their impact on prognosis is presented. An outline of innovative imaging strategies in terms of alternative promising PET radiotracers for use in patients with PCa, and imaging modalities, such as PET/MRI, is also provided.

Imaging biomarkers in primary prostate cancer detection and staging

Ideally, a noninvasive imaging modality able to diagnose and characterize PCa would have a strong clinical impact. Indeed, the availability of reliable imaging techniques would improve the ability to detect more aggressive diseases early. Additionally, imaging biomarkers might play an important role in PCa staging, helping clinicians to stratify patients better according to disease characteristics at diagnosis. This would ultimately provide relevant information regarding the best treatment modality for each patient.

PET/CT in primary prostate cancer detection

The role of PET/CT in primary PCa detection is limited due to the low sensitivity and specificity of this modality in discriminating cancer from normal prostate or hyperplasia. Conflicting results have been reported regarding the use of PET with either ^{11}C-labelled or ^{18}F-labelled choline for the detection of primary PCa, with some studies demonstrating low detection rates and some others higher sensitivity [11]. In a retrospective evaluation performed by de Jong et al. in which patients with biopsy-proven primary prostate carcinoma and benign prostate conditions were evaluated with ^{11}C-choline normal prostate and PCa had mean standardized uptake values (SUV) of 2.3 (1.3 – 3.2) and 5 (2.4 – 9.5), respectively [12–16]. The usefulness of ^{11}C-choline PET/CT for imaging primary PCa was also investigated by Farsad et al. in 36 patients who had biopsy-proven PCa [17]. They found a sensitivity and specificity of ^{11}C-choline PET/CT of 66 % and 81 %, respectively. There was no statistically significant difference in SUV between areas with PCa and areas with high-grade intraepithelial neoplasia. These results were also supported by Sutinen et al. who did not identify any correlations among ^{11}C-choline tumour uptake and grade of differentiation, Gleason score, prostate volume and PSA value [18]. Similarly, Reske et al. did not identify any correlations among ^{11}C-choline SUV, PSA value and Gleason score; however, they did find a correlation between SUV and tumour stage and found that a SUV cut-off value of 2.65 correctly located PCa [12]. Other studies have shown variable sensitivities and specificities of ^{11}C-choline PET/CT for the diagnosis of primary PCa, ranging from 72 % to 87 % and from 62 % to 84 %, respectively, with an overlap of ^{11}C-choline uptake between benign and malignant changes [17, 19].

Although ^{11}C-choline and ^{18}F-choline are the most commonly used tracers for PET/CT in PCa, the value of other radiotracers such as ^{18}F-fluorodeoxyglucose (^{18}F-FDG) and ^{11}C-acetate for PCa detection have also been investigated. Initial analysis of the data from the National Oncologic PET Registry indicated that ^{18}F-FDG PET can affect the clinical management of men with PCa, but this influence is lower than for other cancers. However, these clinical studies have some drawbacks, such as a small and heterogeneous population included and limitations in validation criteria [20]. In addition, as well as for choline derivatives, ^{18}F-FDG uptake in normal prostate, benign hyperplasia and PCa can also overlap making this tracer not useful for diagnosis or staging of clinically organ-confined disease. Moreover, the high level of radiotracer in the adjacent urinary bladder may mask lesions in the vicinity and false-positive results may also occur with prostatitis [21–23]. Despite these drawbacks, some clinical studies have demonstrated that ^{18}F-FDG PET can be useful in PCa in certain clinical circumstances, such as in poorly differentiated primary PCa with high PSA values [24].

Compared with ^{18}F-FDG, and similarly with ^{11}C-choline, the lack of accumulation of ^{11}C-acetate in urine is advantageous for PCa imaging, although a considerable overlap in uptake levels in primary cancer, benign prostatic hyperplasia and normal prostate has been reported for this tracer as well as only a slightly higher uptake in tumour tissue [25]. Interestingly, ^{11}C-acetate has higher sensitivity for primary PCa detection than ^{18}F-FDG [26].

PET/CT in prostate cancer staging

The correct stage of PCa, including definition of primary tumour extension, lymph node (LN) and bone involvement is crucial to establish the correct treatment strategy. Accurate preoperative LN staging at initial diagnosis of PCa is mandatory to guide treatment decisions, since it limits the extent of a pelvic LN dissection (LND) on an individual basis and may even spare some patients from the invasive procedure of an extended pelvic LND [27]. Similarly, the assessment of distant metastases is crucial in patients with high-risk disease in order to identify those who might benefit the most from a treatment with curative intent and those who should receive initial systemic therapies [4]. Choline PET/CT can be efficiently used to assess disease extension in terms of LN and distant metastasis, and also has prognostic significance in PCa staging.

Lymph node staging

Choline is a valuable imaging biomarker for detection of LN disease during staging, providing essential information to choose the most appropriate treatment strategy. Imaging modalities such as CT and MRI may fail to identify metastatic disease in LN smaller than 1 cm because in newly diagnosed PCa up to 80 % of LN metastases can be located in LN of normal size (<8 mm) [28]. This limitation might be overcome by molecular imaging techniques such ^{11}C-choline PET/CT.

Using histology as the gold standard, Schiavina et al. showed that ^{11}C-choline PET/CT has low sensitivity and high specificity (60 % and 98 %, respectively) for LN staging in a population of 57 intermediate-risk and high-risk patients [29]. Similar results have also been found by others [15, 16]. A meta-analysis evaluating the value of PET/CT with choline derivatives in staging PCa confirmed these findings and concluded that for staging, the value of this PET/CT in high-risk patients is still limited and should be performed in selected cases [30]. A further prospective comparison of CT, MRI and ^{11}C-choline PET/CT for preoperative LN staging showed that these three imaging modalities exhibit a rather low sensitivity with less than two-thirds of LN metastases being detected in a patient-based and a field-based analysis. Moreover, in the same study, ^{11}C-choline PET/CT showed the best patient-based specificity, followed by diffusion-weighted MRI (DWI) and CT. In general, overall diagnostic efficacy did not differ significantly among the three imaging techniques [31].

Despite this, PET/CT might have a role in LN staging of selected patients with very high-risk of LN invasion. However, further well-designed studies are needed to identify the groups of patients who might benefit the most from this imaging procedure before primary treatment.

Bone metastasis assessment

PCa has a predilection to metastasize to bone [32] and clinicians who manage patients with PCa have several choices for evaluating the skeleton for metastatic disease, including CT, MRI, bone scintigraphy, ^{18}F-fluoride PET/CT, or ^{18}F/^{11}C-choline PET/CT.

PET molecular imaging, by identifying metastatic disease, has a strong impact on patient management because it helps clinicians choose the best treatment strategy.

PET/CT with sodium ^{18}F-fluoride or ^{11}C-choline can detect more skeletal lesions than bone scintigraphy. There is increasing evidence that sodium ^{18}F-fluoride and ^{11}C-choline could change patient management, either as a first imaging study or as a secondary study after bone scintigraphy [33–36]. Considering that PET/CT is more expensive than planar bone scintigraphy, the demonstration of the cost-effectiveness of PET/CT with sodium ^{18}F-fluoride or ^{11}C-choline compared with bone scintigraphy will depend on the ability to identify groups of patients who would benefit from the higher sensitivity and specificity provided by this modality.

Prognostic evaluation

Few studies have investigated the potential prognostic utility of PET/CT in PCa staging. Challapalli et al. found a good association between baseline ^{11}C-choline SUV and initial PSA levels, and an association between reduction in tumour SUV after neoadjuvant androgen deprivation therapy (ADT) and PSA reduction, suggesting the need for further studies to investigate the prognostic value of choline PET/CT in this setting [37]. Considering alternative radiotracers, Oyama et al. found that primary prostate tumours with a high ^{18}F-FDG SUV have a poorer prognosis than those with a low SUV [38], while Morris et al. showed that an increase in SUVmax of more than 33 % between the baseline and post-treatment scan is able to identify patients with castrate-sensitive metastatic PCa [39]. Interestingly, Meirelles et al. found that SUV is an independent prognostic factor, and indeed they observed that survival was inversely associated with SUVmax, with a median survival of 32.8 and 14.4 months in patients with SUVmax less than or more than 6.10, respectively [40].

Multiparametric MRI in prostate cancer detection

Multiparametric MRI (mp-MRI) can assess both anatomical and molecular features of prostatic lesions. It combines anatomical T2-weighted imaging (T2WI) with functional techniques such as DWI which highlights cell proliferation, dynamic contrast-enhanced imaging (DCEI) which shows neoangiogenesis and MR spectroscopic imaging (MRSI) which displays cell metabolism (Fig. 1) [41, 42]. Currently mp-MRI is considered the most reliable imaging biomarker able to detect suspicious foci of PCa to guide targeted biopsy. In addition, it is able to assess the aggressiveness of the suspected lesion [41].

In an attempt to improve PCa detection, several groups have investigated the combination of different advanced MR techniques in order to improve diagnostic accuracy in PCa localization. In a retrospective single-institution study, 42 patients with elevated PSA levels were investigated. The areas under the receiver operating characteristic curve (A_z) were 0.848, 0.860 and 0.961 for T2WI, DWI, and MRSI, respectively. When all three techniques were used concomitantly, the A_z value increased to 0.978, suggesting that PCa may be more effectively diagnosed using the three techniques combined rather than using them separately [43]. Recently, Haghighi et al. compared the diagnostic performance of DWI and DCEI for PCa detection in a meta-analysis of five studies evaluating these techniques in the same patient cohort using whole-

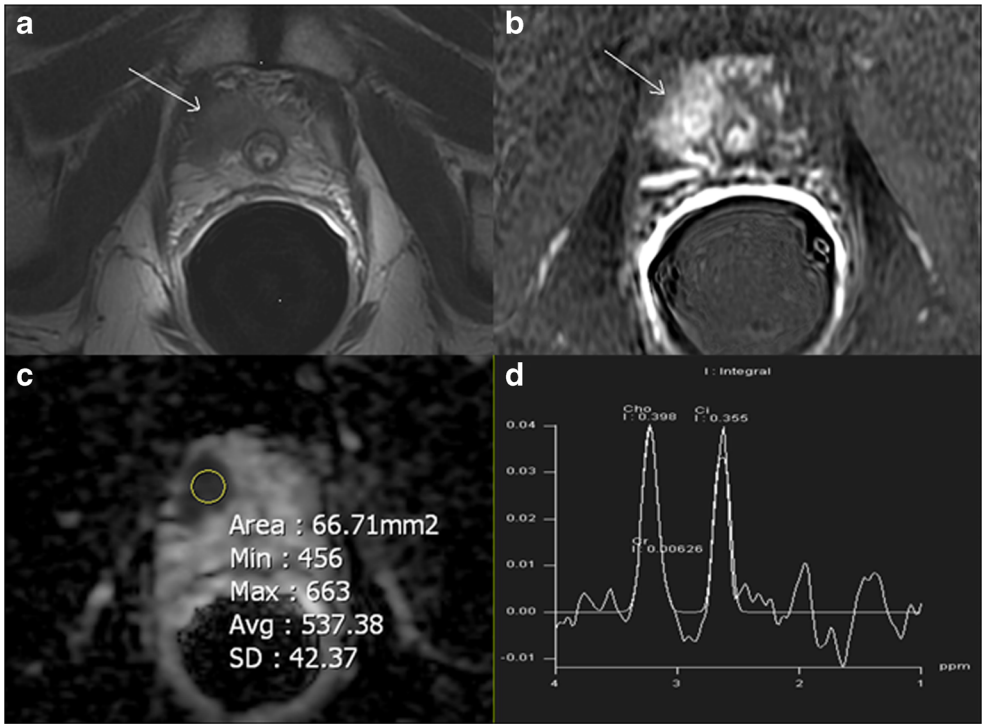

Fig. 1 MR images in a 76-year-old man with four negative transrectal ultrasound-guided biopsies and a PSA serum level of 329 ng/ml. **a** High-resolution axial T2-weighted fast spin-echo image shows a right-sided oval solid hypointense lesion located in the anterolateral aspect of the peripheral zone at the third mid-gland with bulging of the prostatic capsule. **b** Subtracted perfusion image shows avid enhancement of the hypointense zone. **c** Axial ADC map shows intense restricted diffusion (mean ADC 0.5×10^{-3} mm^2/s, consistent with a pattern of intermediate grade aggressiveness). **d** Spectroscopic image shows a high choline peak with a choline + creatine to citrate ratio higher than 1 that is typical of cancerous metabolism. Pathological correlation after radical prostatectomy yielded PCa with a Gleason score of 8 (4+4)

mount step-section histopathology as the standard of reference. The pooled sensitivities were 58.4 % for DWI and 55.3 % for DCEI, the pooled specificities were 89.0 % for DWI and 87.9 % for DCEI, and the A_z values were 0.810 for DWI and 0.786 for DCEI, demonstrating a similar performance of DWI and DCEI [44]. Therefore in routine clinical practice a protocol including T2WI and DWI seems to be sufficient to detect and localize suspicious foci of PCa.

An important drawback of mp-MRI is the difficulty in detecting cancerous foci of PCa with volumes smaller than 0.5 cm^3 and low-risk Gleason score 6 (3+3) [45]. Nevertheless, PCa in patients with organ-confined disease, Gleason score 6 or lower and a tumour volume of 0.5 cm^3 or lower is usually considered clinically insignificant [46]. Thus, the use of mp-MRI might eventually decreases the risk of overdiagnosis and overtreatment, avoiding unnecessary biopsies in individuals with insignificant disease. However, further well-designed studies are needed to address this issue.

Multiparametric MRI in prostate cancer staging

Mp-MRI can enable the evaluation of extracapsular extension, neurovascular bundle (NVB) involvement, seminal vesicle invasion (stage T3) and invasion of adjacent structures such as bladder and rectum (stage T4), which may prevent curative surgery. NVB involvement will preclude NVB-sparing surgery. Conversely, in patients who may otherwise have undergone radical surgery with NVB excision, MRI can accurately show lack of NVB invasion, thus enabling the patient to undergo NVB-sparing surgery [47, 48]. Additionally, patients with locally advanced disease might benefit from adjuvant therapies after primary treatment [49–51].

MRI is also a useful tool for detecting LN metastases, although it has high specificity but low sensitivity for this purpose. The use of node size as the sole criterion is limited because 70 % of metastatic LN in PCa are small (<8 mm) [52]. In order to improve the sensitivity of MRI for the detection of LN metastases, more-sensitive tests have been developed in conjunction with ultrasmall lymphotropic superparamagnetic-based nanoparticles (ferumoxtran-10) that target the reticuloendothelial system. This technology is not yet widely available for clinical use but recent data have shown an overall diagnostic accuracy of 90 % [53]. This technique has shown high sensitivity (65 – 92 %) and excellent specificity (93 – 98 %) in detecting PCa LN metastases, and in non-enlarged small LNs [54].

MRI could also play a role in staging patients with PCa thanks to its ability to depict bone metastases, as demonstrated in several studies showing its high sensitivity and accuracy in this field [55].

Imaging biomarkers in prostate cancer restaging

Recurrence of PCa is suspected when a raise in PSA level is detected after radical treatment that could be determined by either local or distant relapse, or both. Differentiation between the two patterns of relapse is critical to choose the proper treatment strategy [56]. Imaging should be able to discriminate patients with local recurrence that may benefit from salvage local treatment with curative intent from those affected by distant failure that are candidates for systemic therapy. No imaging modality is currently recommended by urological guidelines to be routinely performed to identify the site of recurrence and guide further treatment, especially when PSA values are low [57, 58]. Thus, standard therapeutic options considering any pattern of recurrence after radical treatment are radiation therapy (RT), complete or intermittent ADT, combination of ADT with 5-alfa-reductase inhibitors or early chemo-hormonal approaches [58]. Nonetheless, nowadays there is increasing evidence regarding the possible role of imaging-guided salvage therapies aiming to improve oncological outcomes in patients with local or regional disease relapse [59, 60]. Taken together, these evidences highlight the role of imaging biomarkers in restaging PCa after disease recurrence.

PET/CT in prostate cancer recurrence

Local relapse

Regarding local relapse, choline PET/CT shows low sensitivity particularly in patients with low PSA values [61–64]. This is due to the low sensitivity of this technique because of its limited spatial resolution which hampers visualization of small lesions, and to its limited specificity because choline is also taken up by normal tissue and inflammation [65]. Recently, a sensitivity, specificity and accuracy of 54 %, 92 % and 65 %, respectively, have been demonstrated in a population of 115 patients who underwent ^{11}C-choline PET/CT after RP. In the same cohort, MRI showed a sensitivity, specificity and accuracy of 88 %, 84 % and 87 %, respectively [66].

Lymph node relapse and tailored treatments

As imaging biomarker, the detection of neoplastic LN involvement after primary treatment would be of help in choosing the most appropriate treatment strategy that may include systemic treatment, but also tailored surgery or RT. Kitajima et al. found that PET/CT has a better accuracy than MRI (92 % vs. 70 %) in the detection of pelvic LN metastasis regardless of the PSA value [66]. Despite these good results, LND is still the most reliable approach for LN status assessment [4]. Nevertheless, because of the overall accuracy of choline PET/CT, it has been proposed that pelvic and/or retroperitoneal LND and RT should be performed on the basis of positive choline PET/CT findings [60, 67–71]. Regarding the surgical approach, the first experience was reported by Rinnab et al. in a cohort of 15 patients with biochemical relapse who underwent ^{11}C-choline PET/CT and subsequent open salvage pelvic/retroperitoneal extended LND. Interestingly, the mean time to progression after LND was 23.6 months, and during follow-up after salvage surgery 1 of the 15 patients had a PSA nadir less than 0.1 ng/ml, 3 patients developed bone metastases, and 1 patient had a stable PSA of 0.5 ng/ml. These results suggest that ^{11}C-choline may be useful to detect LN metastases when the PSA level increases after definitive PCa therapy, with some patients benefiting from limited LND [67].

Similarly, Winter et al. evaluated a cohort of patients with the same characteristics. During follow-up three of six patients showed complete permanent PSA remission without adjuvant therapy [70]. Rigatti et al. also found a biochemical response early after salvage surgery in 41 out of 79 patients (56.9 %), and PSA <4 ng/ml, time to biochemical relapse <24 months and negative LNs at the time of RP were predictive of PSA response with biochemical relapse-free survival rates at 3 and 5 years of 27.5 % and 10.3 %, respectively. Clinical recurrence-free survival at 5 years was lower in patients with retroperitoneal LN uptake than in those with only pelvic positive LNs (11 % vs. 53 %; $p<0.001$) [69]. Further analysis performed in a subgroup of this cohort showed overall 8-year survival rates without clinical relapse and cancer-specific mortality of 38 % and 81 %, respectively, with multivariate analysis showing that PSA at the time of salvage LND, biochemical response and retroperitoneal site of uptake on ^{11}C-choline PET/CT were predictors of clinical relapse [60].

As an alternative to surgical treatment, a stereotactic and high-conformal intensity-modulated RT technique, including helical tomotherapy (HTT), planned on the base of the choline findings, has been evaluated as a treatment option with promising results in terms of toxicity, local disease control, and overall and disease-free survival [72–75]. Interestingly, Jereczek-Fossa et al. observed a change in treatment strategy in 22 of 74 patients based on the choline PET/CT results, highlighting the impact of this imaging modality on treatment planning [76]. Similarly, Souvatzoglou et al. confirmed a major impact of ^{11}C-choline PET/CT on RT planning. In 37 PCa patients referred for salvage RT to the prostatic fossa, PET/CT led to an extension of the planned target volume in 13 % of patients due to the detection of more LN sites of relapse. At the end of follow-up, 56 % of patients had a PSA ≤0.2 ng/ml, while 44 % of patients showed biochemical relapse [77].

Würschmidt et al. used choline PET/CT for RT planning in 19 patients and delivered a dose to the prostate bed with a further boost to ^{11}C-choline-positive foci, Specifically, pelvic LN were irradiated with a dose of 45 to 50 Gy with a boost to choline positive LN. At 28 months, biochemical relapse-free survival was 49 % [72]. Interestingly, in patients with

biochemical failure, Casamassima et al. used stereotactic body RT to limited LN recurrences as detected by choline PET, and 3-year overall survival, disease-free survival and local control rates were 92 %, 17 % and 90 %, respectively [73]. One of the most recent studies by Picchio et al. showed the importance of ^{11}C-choline PET/CT as a powerful tool for planning and monitoring HTT in LN relapse after primary treatment, confirming that high-dose hypofractionated HTT with simultaneous integrated boost guided by ^{11}C-choline PET/CT is well tolerated and associated with a high early biochemical response rate. In this study 83 patients with recurrent PCa received radiation to the entire LN chain with a boost to PET/CT-positive LN. Previously irradiated patients and those with unfavourable dose distribution in the organs at risk received RT only to PET/CT-positive LN, and an early, complete and partial biochemical response was observed in 70 % and 12.8 % of patients, respectively [78]. These studies demonstrated that choline PET/CT has great potential for guiding targeted HTT of LN recurrence in PCa patients, and is a useful tool for assessing treatment efficacy and for patient stratification according to their clinical and imaging features enabling selection of those patients who are most likely to respond and benefit from such treatment (Fig. 2). However, urological guidelines do not recommend these targeted approaches, and comparative prospective studies aiming to identify the group of patients who could benefit from these selective therapies and to demonstrate an improvement in patient outcome are warranted.

Currently, there are a limited number of studies evaluating the effect of ADT on choline PET/CT and are not prospectively designed. Although there is still controversy on this issue, the evidence for suspending ADT before performing choline PET/CT is still limited and so it is not recommended in clinical practice [19, 79, 80].

The value of ^{18}F-FDG and ^{11}C-acetate has been investigated in PCa recurrence as well as in PCa detection. A recent review showed an overall limited value of ^{18}F-FDG PET/CT in this setting. In fact, although ^{18}F-FDG PET/CT may detect occult metastatic disease in a small proportion of men who present with biochemical recurrence after primary treatment with curative intent, detection of local recurrence is limited due to an overlapping uptake between tumour recurrence, posttherapy changes and interference from urine activity [81, 82]. Few studies have investigated the performance of ^{11}C-acetate PET/CT in PCa restaging suggesting that this imaging technique has better accuracy for detection of distant and LN recurrence, rather than local recurrence. Moreover, primary treatment could affect the rate of detection with^{11}C-acetate, with a 20 % higher sensitivity in patients treated with surgery than with RT, probably due to the difficulty in ablating the whole prostate gland with RT [38, 83]. Interestingly, the sensitivity of ^{11}C-acetate seems to be related to the PSA value, with a lower sensitivity in patients with a PSA <1 ng/ml than in those with a PSA >1 ng/ml [84].

Prognostic evaluation

Several factors, such as PSA kinetics, Gleason score, previous biochemical failure and pathological stage after RP, can predict outcome [85–87]. In 43 patients who underwent ^{18}F-FDG PET and bone scan prior to experimental therapies for PCa, Meirelles et al. showed that prognosis was inversely correlated

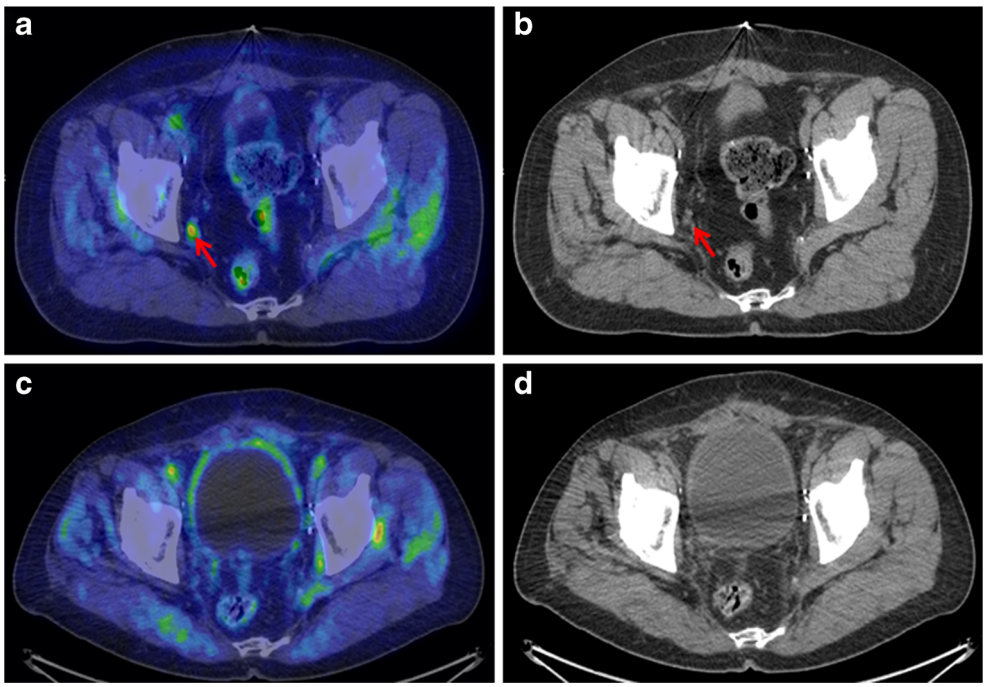

Fig. 2 A 66-year-old patient who underwent ^{11}C-choline PET/CT 1 year after RP because of biochemical recurrence of PCa (PSA 1.67 ng/ml). Transaxial ^{11}C-choline PET/CT image (**a**) and CT image (**b**) show focal LN pathological uptake in the right obturator region (*arrows*). Transaxial ^{11}C-choline PET/CT image (**c**) and CT image (**d**) 8 months after treatment of the LN recurrence with helical tomotherapy show a complete response with no evidence of disease, although PSA level was 1,70 ng/ml

with SUV (median survival 14.4 months with SUVmax >6.10 and 32.8 months with SUVmax ≤6.10, p=0.002) and bone scan index (14.7 months with index >1.27 and 28.2 months with index <1.27, p=0.004). SUV was the only independent predictive factor in multivariate analysis [40]. Some studies have suggested that ^{18}F-FDG PET/CT has prognostic value in castrate-resistant patients, confirming the limited role of this tracer in the evaluation of primary PCa, staging and biochemical recurrence assessment [40, 88].

Giovacchini et al. identified clinical and pathological variables, in addition to PSA level, that are independent predictors of positive ^{11}C-choline PET/CT including locally advanced tumour, pathological LN at initial staging, previous biochemical failure and older age. These findings could represent strong support for clinical practice because, when referring PCa patients for this examination, physicians should not focus only on the PSA value, but should also consider these additional risk factors with specific attention to PSA kinetics [89]. The value of ^{11}C-choline PET/CT in predicting PCa-specific survival has recently been investigated by Giovacchini et al. who evaluated 195 patients with PCa treated with RP who underwent ^{11}C-choline PET/CT for biochemical relapse during ADT. The median survival was 11.2 years among patients with positive ^{11}C-choline PET/CT and 16.4 years among patients with negative ^{11}C-choline PET/C. According to the site of positivity, patients with pathological uptake in the prostate bed or in pelvic/retroperitoneal LN had longer prostate-cancer specific survival than patients with pathological tracer uptake in the skeleton [90].

Multiparametric MRI in prostate cancer recurrence

Mp-MRI can currently be considered as the most reliable imaging biomarker for detecting local PCa recurrence in patients with biochemical failure after RP and PSA values for which PET/CT is not indicated (0.2 – 1 ng/ml) [91, 92]. Indeed, mp-MRI after RP is very useful for discriminating between locoregional relapse and small amounts of healthy residual glandular tissue, scar/fibrosis and granulation tissue, and it may even enable assessment of the aggressiveness of nodule recurrence by means of ADC values. In patients scheduled for local salvage external beam RT (EBRT) after RP, accurate anatomical localization of tumour deposits within the postprostatectomy bed may allow individualization of the field of irradiation maximizing efficacy and minimizing toxicity to normal surrounding tissues. In this setting mp-MRI findings could be used to apply a stereotactic boost to the recurrence site, potentially improving local disease control and avoiding further locoregional relapses over time. Furthermore, the differential diagnosis between healthy residual glandular tissue and locoregional neoplastic recurrence is of crucial importance for radiation oncologists because the RT delivered to the prostate bed is quite different [91, 92].

In patients with local recurrence after definitive EBRT, if local salvage therapy is not performed early, the median time to development of distant metastases is approximately 3 years, so there is in an increasing need for imaging techniques able to identify and localize recurrent PCa in order to perform effective salvage therapy with minimal complications. Moreover, at present mp-MRI is widely considered to be the best choice to detect PCa recurrence in patients with biochemical progression after definitive RT [92].

Future perspectives

Research in the field of new radiotracers and new imaging techniques that could possibly improve the diagnosis and management of PCa patients is vivid and active. Although choline PET/CT is currently considered a valuable tool in the management of PCa, other radiotracers have been investigated with the aim of overcoming the intrinsic limits of ^{11}C-choline and ^{18}F-choline. A radiolabelled leucine analogue, 1-amino-3-fluorocyclobutane-1-carboxylic acid in the 'anti' configuration (^{18}F-FACBC), can be used to depict amino acid transportation and its uptake in PCa has been shown. Since only a small fraction of ^{18}F-FACBC is excreted through the urinary tract early after injection, its imaging characteristics seem to be favourable in the evaluation of prostate disease [93, 94]. Published data indicate that ^{18}F-FACBC can be successfully used in the assessment of primary and metastatic PCa, and preliminary results indicate that ^{18}F-FACBC may be superior to ^{11}C-choline for the identification of disease recurrence in the setting of biochemical failure (Fig. 3) [95–99].

In recent years, efforts have been made to develop ligands to target prostate-specific membrane antigen (PSMA) which is known to be overexpressed in PCa tissue. Some results have already been reported regarding the clinical use of PET imaging with ^{68}Ga-labelled ligands of PSMA. Due to its better signal to background ratio than choline derivatives, improvements in contrast and sensitivity in lesion detection, including small LN metastases, central bone and liver metastases, have been reported, even in patients with low PSA levels [100–104].

Additionally, one of the main advantages of ^{68}Ga-labelled PSMA ligands is that no cyclotron is required since ^{68}Ga can be extracted from a commercially available ^{68}Ge/^{68}Ga radionuclide generator, while radiolabelled choline tracers require isotopes produced by a cyclotron.

Regarding the possible improvement and advantages that could derive from the use of new technologies applied to imaging, combined PET/MRI is surely the most promising technique that could have a major impact on clinical management of PCa patients [105, 106]. While combined PET/CT is a well-established method for oncological imaging,

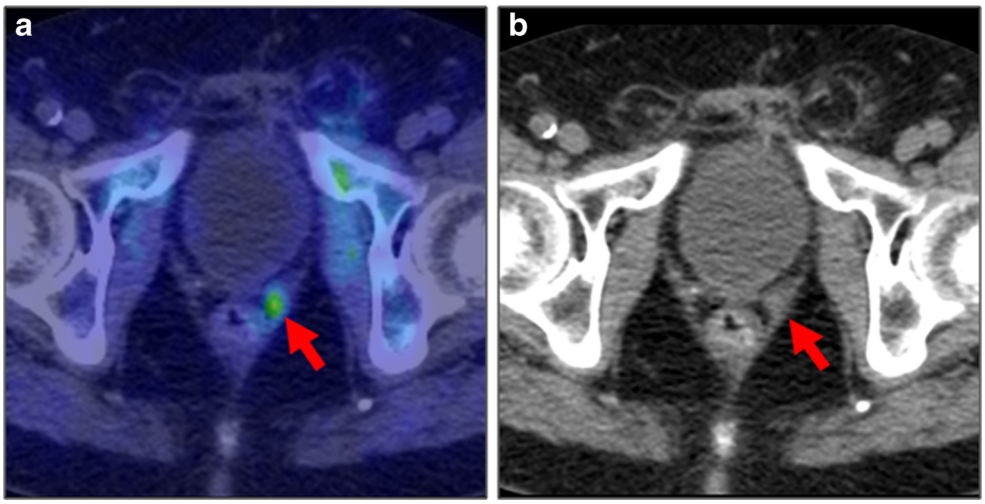

Fig. 3 A patient previously treated with RP (stage pT3aN1) and adjuvant RT for PCa experienced biochemical recurrence (PSA 1.2 ng/ml). The ^{18}F-FACBC PET/CT image shows focal pathological uptake (**a**, *arrow*) corresponding to a perirectal LN on the CT transaxial image (**b**, *arrow*)

simultaneous PET/MRI has only recently been introduced in few centres. Although optimal attenuation correction still remains a challenge, combined PET/MRI of the prostate has the advantage of combining high-resolution prostate images and metabolic/molecular imaging. Simultaneous acquisition of mp-MR and PET images with an appropriate radiotracer may be particularly valuable for identifying high-yield candidate biopsy sites that could reduce the rate of false-negative initial and repeat biopsies [107]. Moreover, PET/MRI might improve salvage RT planning by enabling more precise target volume delineation of local recurrence as well as of LN with PCa involvement [108]. Furthermore, image acquisition times have been shortened, thus allowing whole-body MRI examinations with high spatial resolution in less than 1 h [109].

Initial results with the use of PET/MRI in PCa have been published [110–113], and are particularly promising with regard to the detection of primary tumour, bone involvement and local PCa relapse. When compared with choline PET/CT, lower SUVs with PET/MRI have been observed probably because of the different techniques applied for attenuation correction [105, 106]. Preliminary studies including small cohorts of patients have also evaluated the possible role of PET/MRI with alternative radiotracers such as ^{68}Ga-labelled PSMA, but the findings still need further assessment and confirmation [101, 102, 114]. PET/MRI, simultaneously assessing multiple tumour parameters is an innovative tool that could potentially improve tumour detection and characterization in the settings of staging and restaging, being also able to guide treatment planning on a patient basis and also providing better response assessment [108, 115].

Conclusion

Although PSA remains the least expensive and most widely used biomarker for screening and treatment monitoring in PCa, it is not able to provide a clear distinction between local and distant disease. PET/CT has some limitations in the detection of primary PCa, but it is a reliable technique for investigating disease extension during staging and particularly restaging, providing accurate results on LN and distant disease localization. Moreover, its role in treatment planning and monitoring has been largely validated, and initial results on the prognostic role of this technique in recurrent PCa have recently been reported. Mp-MRI is an accurate technique for depicting even small foci of PCa and so it is an efficient tool for diagnosis and detection of local recurrence after treatment, provides functional information on tumour characteristics and aggressiveness, and is very accurate in discriminating PCa recurrence form posttreatment scar and fibrosis.

Testing of promising new radiotracers in PCa indicates that they could play a role in overcoming some of the limitations that are currently observed with the most widely used radiotracers in PCa, namely ^{18}F-choline and ^{11}C-choline. Moreover, the recent introduction into clinical practice of PET/MRI, that combines metabolic data with a high-resolution technique such as mp-MRI, will almost certainly enhance the accuracy of PCa imaging.

Conflicts of interest None.

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