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REVIEW ARTICLE

PET imaging in prostate cancer, state of the art: a review of ^{18}F-choline and ^{11}C-choline PET/CT applications

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Abstract The aim of this paper is to review the role of ^{18}F-choline or ^{11}C-cholinePET/CT in prostate cancer patients for diagnosis, staging and restaging in case of biochemical recurrence and on the use of ^{18}F-choline or ^{11}C-choline PET/CT for metastases directed salvage therapies and in castrate-resistant patients treated with systemic therapy. A literature search was performed, and articles related to ^{11}C-choline and ^{18}F-choline PET/CT in prostate cancer staging and biochemical relapse were identified. Search terms were: "PET" and "PET/CT", "^{11}C-choline", "^{18}F-choline", "prostate cancer staging", "lymph node staging" "biochemical recurrence". We have reported the results of the most relevant publications following the criteria of clinical relevance, confirmations of choline PET/CT findings with histology, other imaging methods or clinical follow-up. Moreover, we have briefly reported about the use of ^{18}F-choline or ^{11}C-choline PET/CT for prostate cancer diagnosis and to monitor castrate-resistant prostate cancer (CRPC) patients treated with systemic therapy. In lymph node and distant staging choline, PET/CT showed low sensitivity but, in most of the cases, a relatively high specificity. In case of biochemical recurrence, PSA absolute value and PSA kinetics confirmed their strict correlation with choline PET/CT findings. Choline PET/CT resulted to be very useful to address salvages therapies, especially in the early phases of biochemical recurrence. The use of choline PET/CT in CRPC should be more deeply investigated. At the moment, its use in the diagnosis of prostate cancer is not recommended. ^{18}F-choline or ^{11}C-choline PET/CT provides useful information to clinicians mostly in case of biochemical recurrence, while the low sensitivity limits its use during staging.

Keywords Prostate cancer · Choline PET/CT

Introduction

Prostate cancer (PCa) is the most common cancer in men [1]. Suspicion for PCa is most commonly based on digital rectal examination (DRE), serum levels of prostate-specific antigen (PSA) and trans-rectal ultrasound (TRUS) [2]. When histology confirms the presence of PCa, patients can be staged with different imaging procedures to evaluate tumor extension and to exclude the presence of distant spread [2]. Trans-rectal ultra-sound (TRUS), magnetic resonance imaging (MRI), computerized tomography (CT) and bone scintigraphy (BS) are the most used imaging modalities in PCa patients. ^{18}F or ^{11}C labeled choline is the most worldwide used radiopharmaceutical in molecular imaging, for the diagnosis, staging and re-staging of PCa patients. Positron emission tomography (PET) using choline labeled with ^{11}C or ^{18}F provides additional information compared to other imaging methods [3].

The aim of this paper is to review the role of ^{18}F-choline or ^{11}C-choline PET/CT in PCa patients for staging and restaging in case of biochemical recurrence after primary treatments.

A comprehensive PubMed literature search was performed, and articles related to ^{11}C-choline and ^{18}F-choline PET/CT in prostate cancer staging and biochemical relapse were identified, up to April 2016. Search terms were: "PET", "PET/CT" or "positron emission tomography/computed

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tomography", "^{11}C-choline", "^{18}F-choline", "prostate cancer staging", "lymph node staging" and "biochemical recurrence". Overall, 320 studies were retrieved.

We have analyzed the results of the most relevant publications who reported data about the performance of ^{18}F-choline or ^{11}C-choline PET/CT in prostate cancer diagnosis, lymph node staging or restaging in case of biochemical recurrence. We analysed the publications were patient populations were accurately selected (prospectively or retrospectively) and were results of ^{18}F-choline or ^{11}C-choline PET/CT were validated by histology, by other imaging methods or by clinical follow up. According to these criteria, we finally selected 33 works that were judged clinically relevant. Of these 33 studies, 13 were focused on staging (7 on the use of PET/CT in prostate cancer diagnosis and 6 were focused on lymph node staging) and 20 on (Fig. 1) biochemical recurrence after primary treatment.

Moreover, we have briefly focused our attention on the use of ^{18}F-choline or ^{11}C-choline PET/CT for prostate cancer diagnosis, and to monitor castrate-resistant prostate cancer (CRPC) patients treated with systemic therapy.

Finally, we would like to underline that in this field the validation of choline-PET/CT findings stills remains a major problem. As for all the others imaging methods, the validation of choline-PET/CT findings should be performed with histology as reference standard. However, this is feasible and available only in certain circumstances, such as lymph node staging before surgery, local relapse or some bone or some lymph node (Fig. 2) lesions located in accessible regions. That is why criteria of selection only based on histology as validation standard are not possible.

PET/CT in prostate cancer staging

Staging prostate cancer is crucial to establish the correct treatment strategy, since it should guide further decisions [2]. The detection of nodal or distant metastases should select patients who might benefit the most from a curative treatment, and those who should receive systemic therapies [2]. In lymph-nodal staging, Schiavina et al. [4] showed that ^{11}C-choline PET/CT has low sensitivity but high specificity (60–98 %, respectively) in a population of 57 intermediate- and high-risk patients.

These data were confirmed by Contractor et al. [5] who showed a sensitivity of 40 % and a specificity of 98 % in nodal staging using ^{11}C-choline PET/CT. Poulsen et al. [6] used ^{18}F-choline-PET/CT to stage 210 intermediate- or high-risk patients. Authors showed a patient based sensitivity and specificity of 73 % and 87 % respectively, while a sensitivity and specificity of 56 % and 94 % have been found on a lymph node basis. Van den Bergh et al. [7] prospectively assessed sensitivity, specificity, PPV of ^{11}C-choline PET/CT and DW-MRI for nodal staging in patients with high risk for nodal involvement. The authors enrolled 75 patients who were N0 at CT. Thirty seven of 75 patients
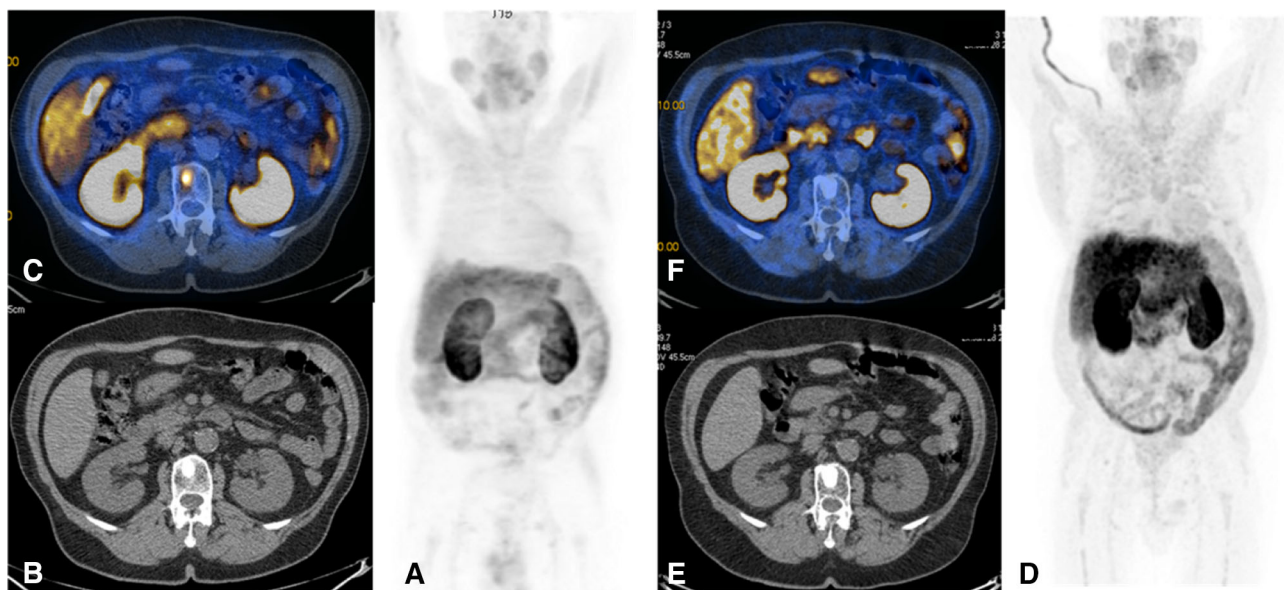

Fig. 1 Sixty-one-year-old patient; GS 4 + 4; T3N1Mx; PSA 10 ng/ml at presentation radical prostatectomy (RP) as primary treatment. Biochemical recurrence 18 months after RP. PSA increased up to 1.2 ng/ml (PSAdt 4.5 months) when a ^{11}C-choline PET/CT has been performed. ^{11}C-choline PET/CT shows one area of intense uptake in an osteoblastic lesion in D12 (SUVmax 6.3). a MIP images; b CT images; c fused images. ^{11}C-choline PET/CT performed after PET-guided EBRT (60 Gy) shows complete metabolic response (d MIP images; f fused images), while the osteoblastic lesion evident on CT images e increased in volume and density. PSA dropped to 0.2 ng/ml after EBRT
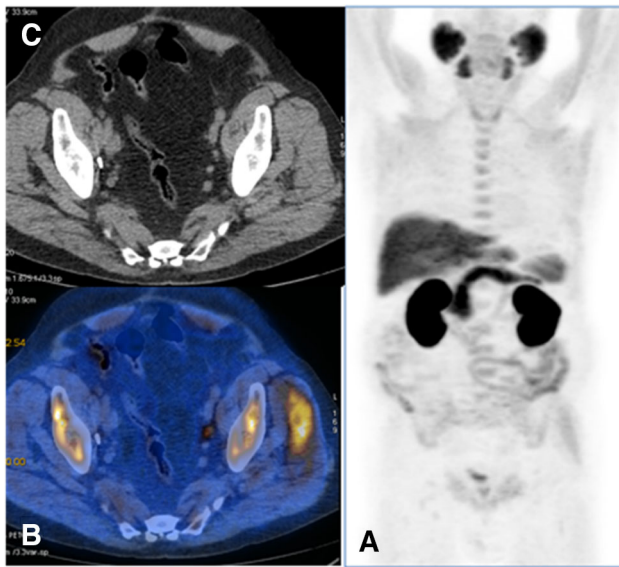
Fig. 2 Sixty-two-year-old patient; GS 4 + 3; T3N0Mx; PSA 9 ng/ml at presentation. Radical prostatectomy (RP) as primary treatment. Biochemical recurrence 28 months after RP. At the time of ^{11}C-choline PET/CT PSA was 0.9 ng/ml; PSAdt 5 months. Area of increased uptake in a left external iliac lymph node consistent with relapse confirmed after salvage pelvic lymph node dissection. **a** MIP images, **b** fused images, **c** CT images

(49 %) resulted positive at histology. On a patient-based analysis, ^{11}C-choline PET/CT showed a sensitivity of 18.9 % and a PPV of 63.6 %, while DW-MRI showed a sensitivity of 36.1 % and a PPV of 86.7 %. On a region-based analysis, ^{11}C-choline PET/CT showed a sensitivity of 8.2 % and a PPV of 50.0 % while DW-MRI showed a sensitivity of 9.5 % and a PPV of 40.0 %.

Recently, Evangelista et al. [8] published a meta-analysis evaluating the role of ^{18}F-choline or ^{11}C-choline PET/CT in staging prostate cancer. Most of the papers analyzed confirm preliminary findings assessing a low sensitivity but high specificity for ^{18}F-choline or ^{11}C-choline PET/CT for nodal staging. Pooled sensitivity and specificity were respectively 49 and 95 % on a patient basis.

According to the most relevant literature, the use of ^{18}F-choline or ^{11}C-choline PET/CT for lymph node staging should be reserved to high and very high-risk patients according to nomograms to minimize the number of false-negative results. This approach has been recently suggested by Evangelista et al. [9] who reported an overall accuracy of ^{18}F-choline PET/CT for lymph node involvement of 83 % for high-risk patients compared to only 33 % for intermediate-risk patients.

However, in conclusions of this chapter, it should be taken into consideration that even in patients with high risk for positive lymph nodes at presentation and even in highly selected patient population (for example in the study published by Van den Bergh [7]), poor sensitivity and poor

PPV may occur either on a patient- or lymph node-based analysis. The main reason for choline PET/CT false-negative findings is the size of nodal metastatic deposit, since it is very unlikely that PET/CT may detect lesions smaller than 5 mm. On the contrary, the main reason for false-positive findings is the presence of reactive lymph nodes that may show (Fig. 3) increased choline uptake.

PET/CT in prostate cancer re-staging: PET/CT in the detection of local, lymph node and bone lesions

When a biochemical relapse (BR) occur, differentiation between the two patterns of relapse, local and/or distant is crucial to choose the proper treatment strategy [10]. The role of imaging should be to discriminate patients with single or oligo-metastatic disease that may benefit from salvage treatments with curative intent, from those affected by multi-spread of the disease that are ideal candidates for systemic therapy. None of the most used imaging modalities gave satisfactory results to identify the site of recurrence and guide further treatments [2], except MRI in the detection of local relapse in the prostatic fossa [11]. Thus, therapeutic approaches are radiotherapy in the prostatic fossa, complete or intermittent androgen deprivation therapy (ADT), or chemo-hormonal treatments [2]. In the last years, however, there is an increasing evidence of the role of image-guided salvage therapies in patients showing single or oligo-metastatic disease [12, 13].

Choline-PET/CT showed low sensitivity in the detection of local relapse after primary treatment, especially at low PSA values. 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 radical prostatectomy in comparison with a sensitivity, specificity and accuracy of 88, 84 and 87 %, respectively, as shown by MRI [14].

These results are in line with previous findings reported by many authors [11, 15, 16] in which the sensitivity for local recurrence either using ^{18}F-choline or ^{11}C-choline PET/CT ranges from 50 to 60 % approximately.

On the contrary, the sensitivity for choline PET/CT for the detection of lymph-nodal involvement after primary treatment seems to be higher than other imaging methods. Kitajima and colleagues showed a better accuracy of ^{11}C-choline PET/CT compared to MRI (92 vs 70 %) in pelvic lymph node metastasis detection, regardless of PSA values [14].

Reliable information about the sensitivity of ^{18}F-choline or ^{11}C-choline PET/CT in the detection of pelvic or abdominal LNs is provided by some works performed with the aim to guide salvage pelvic lymph node dissection (S-PLND) after RP [12, 17, 18].
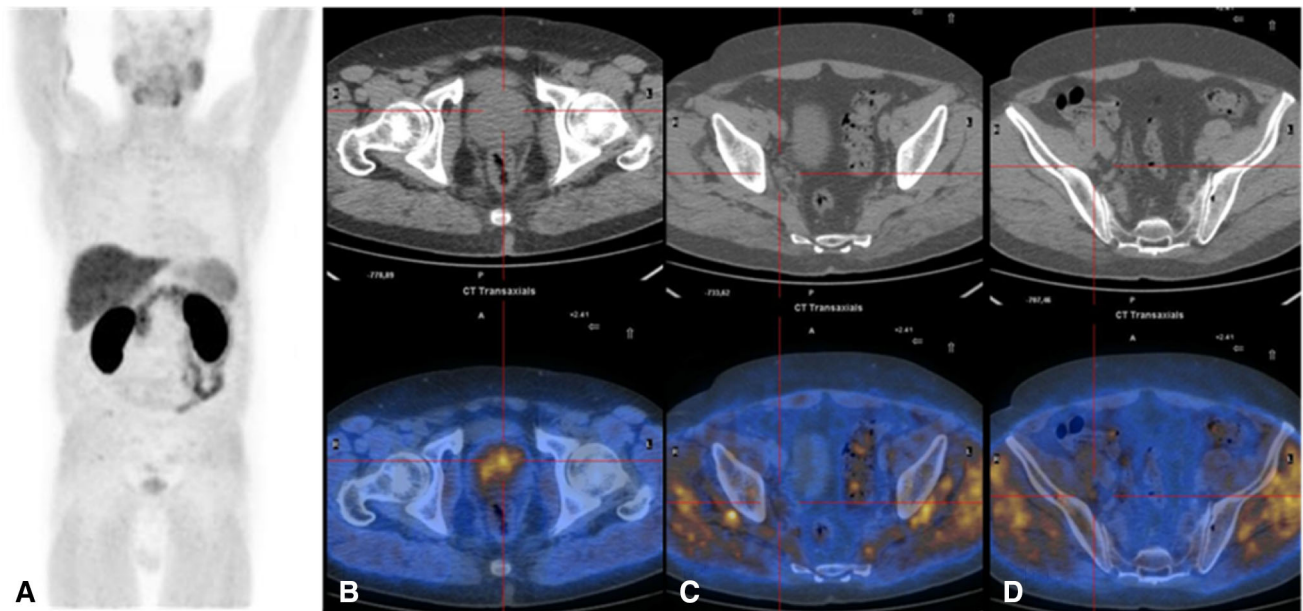
Fig. 3 Sixty-nine-year-old patient; GS 4 + 4 (biopsy); T3a; PSA 12 ng/ml at presentation. Staging ^{11}C-choline PET/CT in an high risk patient. **a** MIP images; ^{11}C-choline PET/CT shows intense uptake (SUVmax 5.8) in the prostate (**b** fused images of the prostate gland); ^{11}C-choline PET/CT shows no significant increased uptake in two *right* iliac lymph nodes (**c** and **d** fused images of the *right* iliac lymph nodes). After surgery, 3/18 lymph nodes removed resulted positive: two in the *right* iliac chain and one in the *left* iliac chain

Tilki et al. [17] studied, with ^{18}F-choline PET/CT, 56 PCa patients with BR after radical prostatectomy who subsequently underwent bilateral pelvic and/or retroperitoneal lymph-adenectomy based on positive ^{18}F-choline-PET/CT findings. Of 1149 lymph nodes that were removed and histological evaluated, 282 (24.5 %) harbored metastasis. On a lesion-based analysis, ^{18}F-cholinePET/CT showed sensitivity, specificity, PPV, and NPV of 39, 95, 75, and 83 %, respectively.

The performance of ^{11}C-choline PET/CT and bone scan was compared by Picchio et al. [19] in 78 patients with BR. The author showed a little lower sensitivity for ^{11}C-cholinePET/CT compared to bone scan (89 vs 100 %), but a significant higher specificity (98 vs 75 %).

Fuccio and colleagues [20] performed a comparison between ^{11}C-choline PET/CT and bone scan in 25 patients with BR showing only one lesion on bone scintigraphy. ^{11}C-choline PET/CT detected multiple sites of relapse in 44 % of patients, with a sensitivity and specificity of 86 and 100 %, respectively. Beheshti et al. [21] studied 38 patients with the aim to compare the accuracy of ^{18}F-choline and ^{18}F-fluoride PET/CT for detecting bone metastases. The authors reported a sensitivity, specificity and accuracy of 74, 99 and 85 % for ^{18}F-choline-PET/CT, and a sensitivity, specificity and accuracy of 81, 93 and 86 % for ^{18}F-fluoride PET/CT.

It is interesting to underline that the uptake of choline in bone lesions may vary depending on the type of lesions. Beheshti et al. [22] compared the uptake of ^{18}F-choline-PET/CT in 70 patients during staging or restaging PCa and compared these results with morphological changes identified on CT. The authors showed that lytic lesions had higher metabolism than sclerotic lesions.

Ceci and colleagues [23] confirmed these results in a group of 140 patients during BR studied with ^{11}C-choline PET/CT. The authors analyzed 304 bone lesions (184 osteoblastic, 99 osteolytic, and 21 bone marrow lesions), showing a significant difference of SUVmax between osteosclerotic (lower values) and osteolytic (higher values) lesions.

In case of biochemical recurrence, ^{18}F-choline or ^{11}C-choline PET/CT demonstrated a significant clinical impact on patients' management. In three papers recently published from three different single institution series, it was demonstrated that choline-PET/CT led to a change in the decision-making process in approximately the 50 % of cases [24–26].

Finally, in a recent meta-analysis by Fanti et al. [27], the authors analyzed (Table 1) 29 studies that enrolled 2686 patients. The authors reported for ^{11}C-choline PET/CT a detection rate for any site of relapse of 62 % (95 % CI 53–71 %) with a pooled sensitivity of 89 % and a pooled specificity of 87 %.

PET/CT in prostate cancer re-staging: PET/CT as a guide for salvage therapies

The first large prospective study has been published by Rigatti et al. [18]. The authors performed a ^{11}C-choline-

Table 1 ^{18}F-choline or ^{11}C-choline PET/CT in lymph node staging

Author (refs.)	Year	Pts (n)	Isotope	Risk group	Sensitivity (%)	Specificity (%)	Reference standard
Schiavina et al. [4]	2008	57	[11]C	Intermediate high	60	98	Histology
Contractor et al. [5]	2011	26	[11]C	High	40	98	Histology
Poulsen et al. [6]	2012	210	[18]F	Intermediate high	73	87	Histology
Van den Bergh et al. [7]	2015	75	[11]C	High	18	63	Histology
Evangelista et al. [9]	2015	48	[18]F	Intermediate high	66	93	Histology
Evangelista et al. [8][a]	2013	441	[11]C [18]F	Intermediate high	49	95	Histology

Results are reported on a patient-based analysis

[a] Meta-analysis

PET/CT guided salvage lymph node dissection (S-LND) in a series of 79 patients. Patients had no more than two positive lymph node lesions at ^{11}C-choline-PET/CT. The authors reported an early biochemical response after S-LND in 41 out of 79 patients (56.9 %) showing that PSA <4 ng/ml, time to relapse (TTR) <24 months and N0 at the time of RP were predictive of PSA response with biochemical relapse-free survival rates at 3 years of 27.5 % and biochemical relapse-free survival rates at 5-year of 10.3 %. Five-years clinical recurrence-free survival was lower for patients with positive retroperitoneal LNs at ^{11}C-choline-PET/CT versus patients with only pelvic ^{11}C-choline-PET/CT positive nodes (11 vs 53 %; $p < 0.001$).

Suardi et al. [12] performed further analysis on a sub-group of 56 patients of this series. The authors showed an overall 8-year clinical relapse- and cancer-specific mortality-free survival rates of 38 and 81 %, respectively. Multivariate analysis showed that PSA higher than 2 ng/ml at S-LND and the presence of retroperitoneal positive lymph nodes on ^{11}C-choline-PET/CT were predictors of clinical relapse. Karnes and colleagues [28] had encouraging results in a group of 52 patients treated with S-LND after primary RP. After a median follow-up of 20 months, 57.7 % (30 of 52) patients had a PSA value lower than 0.2 ng/ml, while 75 % (39 of 52) were free of systemic progression and 96.2 % (50 of 52) were alive.

[18]F-choline or ^{11}C-choline PET/CT-guided salvage radiation therapy (S-RT) using high conformal technique by intensity-modulated RT (IMRT), or helical tomotherapy (HTT), can be also performed in patients showing single or oligometastatic disease [29, 30]. The optimal timing for S-RT to obtain the best chance of cure would be when the tumor burden is low, that is, when PSA first reaches detectable levels during biochemical recurrence [10].

Würschmidt et al. [31] performed an S-RT on ^{11}C-choline PET/CT positive findings of 19 patients during biochemical recurrence. Almost the half of the patients (49 %) were biochemical relapse free after 28 months of follow-up.

Picchio et al. [32] used ^{11}C-choline PET/CT to guide HTT in 83 patients showing LN relapse after primary treatment. The authors achieved an early biochemical response in 70 % of cases. The same group of authors recently published [33] a study about a cohort of 68 patients with BCR after radical therapy and treated with HTT in correspondence of the pathologic choline LN uptake. The 24 months overall survival, loco-regional relapse-free survival, clinical relapse-free survival and BFS were 87, 91, 51, and 40 %, respectively.

Berkovic et al. [34] investigated whether repeated stereotactic body RT (SBRT) of oligometastatic disease is able to defer the initiation of ADT in patients with low-volume metastases. They enrolled 24 recurrent PCa patients with BCR after radical therapy and 1–3 synchronous metastases (bone and/or LNs) assessed by ^{18}F-choline-PET/CT. Patients were treated with repeated SBRT and the ADT-free survival defined as the time interval between the first day of SBRT and the initiation of ADT was the primary end point. They concluded that repeated salvage SBRT is feasible, well tolerated and defers palliative ADT with a median of 38 months in patients with limited bone or LN PCa metastases.

In conclusion, despite S-RT or S-LND, many patients will experience disease progression soon after treatment [12, 13, 18, 31–33]. For this reason, all efforts should be attempted to exclude the presence of metastasis already present at the time of salvage treatments and not included in the planned target volume (PTV) or that could not be removed by an S-LND. In this regards, Castellucci et al. [35] a cohort 605 recurrent PCa patients showing low PSA values (PSA range 0.2-2 ng/mL) studied with ^{11}C-choline-PET/CT after RP and listed for S-RT in the prostatic bed. ^{11}C-choline-PET/CT detected a disease limited to the pelvis in the 13.7 % of patients, while the presence of an extra-pelvic disease was observed in the 14.7 %. The authors observed that the ^{11}C-choline-PET/CT detection rate increased dramatically in patients with a PSAdt lower than 6 months (^{11}C-choline-PET/CT detection rate 47 %) and in patients with ongoing ADT (^{11}C-choline-PET/CT detection rate 46 %). The authors concluded that ^{11}C-choline-PET/CT should be performed before salvage

therapies, especially in those patients showing fast PSA kinetics to exclude the presence of distant lesions that could not be removed with an SLND or included in the planned PTV.

In conclusions of this chapter, the use of ^{18}F-choline or ^{11}C-choline PET/CT to guide aggressive therapies in patients with limited disease is increasing. We would like to stress, once again, that an early detection of metastatic disease is crucial for the outcome of the patients. So, despite the limitation that choline PET/CT may result negative in a significant number of patients in the early phases of BCR when PSA values are low, this is the situation where the patients have still many open options and where the decision of a systemic or aggressive therapy should be taken. The detection of few lymph node or bone metastasis by ^{18}F-choline or ^{11}C-choline PET/CT (oligometastatic patients) should guide the most appropriate treatment and may lead to a better outcome of these patients. This has to be assessed in future prospective studies.

PET/CT in prostate cancer diagnosis

Multi-parametric MRI using T2-weighted–diffusion weighted and dynamic contrast enhanced imaging has the highest accuracy among any other modality in the evaluation of intra-prostatic cancer [36]. A study on a sextant-based comparison with histology was performed for the first time by Farsad et al. [37] in 2005. The authors investigated the potential usefulness of ^{11}C-choline PET/CT for detection and localization of tumors within the prostate in 36 patients scheduled for surgery. ^{11}C-choline PET/CT showed a sensitivity of 66 %, a specificity of 81 %, an accuracy of 71 %, a positive predictive value (PPV) of 87 % and a negative predictive value (NPV) of 55 %. In conclusion, ^{11}C-choline PET/CT was able to demonstrate foci of prostate cancer in all patients, but with a high false-negative rate on a sextant basis. In the following years, many other works substantially confirmed these findings [38–40], assessing for ^{11}C-choline PET/CT a sub-optimal sensitivity (especially in the presence of small foci of cancer) and also a sub-optimal specificity, mainly due to the very frequent presence of non-neoplastic conditions within the prostate gland. More recently, these data were confirmed by Bundschuh et al. [41], who correlated the uptake of ^{11}C-choline PET/CT in the prostate gland with histopathology. The results were relatively poor since only 46 % of histo-pathological positive lesions showed an increased choline uptake. Also Grosu et al. [42] could not discriminate with ^{11}C-choline PET/CT between the presence of malignant versus normal prostate tissue. ^{11}C-choline uptake has been found in both neoplastic and non-neoplastic tissue and often the uptake was even higher in non neoplastic-tissue.

Finally, Van den Bergh et al. [43] compared ^{11}C-choline PET/CT and MRI for the detection of intra-prostatic tumor. The authors showed that sensitivity increased, but specificity decreased combining both modalities indicating that additional information provided by ^{11}C-choline PET/CT is of limited value.

In conclusion, according to these poor results, ^{18}F-choline or ^{11}C-choline PET/CT cannot be recommended as the first-line screening imaging procedure in patients with high risk of prostate cancer or in patient candidates for active surveillance. ^{18}F-choline or ^{11}C-choline PET/CT showed moderate sensitivity, particularly when small carcinomas are present (below the limits of choline PET/CT resolution), but it also has shown moderate specificity since differentiation between benign changes (for example prostatitis or benign prostatic hyperplasia BPH) and malignant tissue is not always possible.

PET/CT in castrate resistant prostate cancer

Prostate cancer patients may develop a resistance to the ADT and, consequently, the hormonal blockade loses its protective effect on the tumor cells growth [10]. This condition of castrate resistant prostate cancer (CRPC), when metastatic (mCRPC), is associated with a median overall survival that ranges between 2 and 3 years and at this stage, palliation is the goal of any treatment [10]. Many different palliative therapies could be used, including systemic chemotherapy (e.g., docetaxel and cabazitaxel) and new antiandrogenic therapies (e.g., abiraterone and enzalutamide) [10]. However, a consensus about the optimal timing and different scheme treatments has not been reached [10]. The main problem for clinicians is the lack of accuracy demonstrated by PSA for predicting the response to therapy in mCRPC [10].

Ceci et al. [44] investigated a cohort of 61 mCRPC patients with ^{11}C-choline-PET/CT performed before and after treatment to assess the response to docetaxel. The authors compared the response assessed by ^{11}C-choline-PET/CT to docetaxel to the response assessed with PSA. The progression disease (PD) was defined as the appearance of a new ^{11}C-choline-PET/CT positive lesion, while the PSA response was defined as a decrease of ≥50 % of the PSA values before and after chemotherapy. The main finding of the study was that ^{11}C-choline-PET/CT PD was observed in the 44 % of patients presenting PSA response after docetaxel. It is to underline that a higher tumor burden (expressed as more than ten PET-positive bone lesions before docetaxel) was significantly associated with an increased probability of PD after treatment. Recently, abiraterone and enzalutamide were proposed as new generation ADT, with good results in terms of biochemical response and pharmacological related effects [18]. De

Giorgi et al. [45] used ^{18}F-choline-PET/CT for evaluating the early response to treatment with abiraterone and enzalutamide in two cohorts of mCRPC patients. The authors confirmed that the response assessed with ^{18}F-choline PET/CT was associated with a more favorable overall survival than a PSA response of ≥ 50 %. Maines et al. [46] studied with ^{18}F-choline-PET/CT 30 mCRPC patients treated with enzalutamide. The authors observed that SUVmax values measured at ^{18}F-choline-PET/CT performed before enzalutamide were significantly related with biochemical, radiological and overall survival. In the next future, prospective well-designed trials should answer the question if ^{18}F-choline or ^{11}C-choline PET/CT could be able to predict the response to treatment and predict the progression-free survival, beyond the poor information provided by the variation of PSA levels. The information that ^{18}F-choline or ^{11}C-choline PET/CT could give, when performed before the administration of therapy (evaluation of the tumor burden) or during and after treatment (assess the objective response), could provide very useful information for the clinicians to choose the most appropriate treatment strategy.

Compliance with ethical standard

Retrospective studies For this type of study, formal consent is not required.

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