Review Article

Positron-emission tomography imaging in urological oncology: Current aspects and developments

Isabel Rauscher, Matthias Eiber, Wolfgang A Weber, Jürgen E Gschwend, Thomas Horn and Tobias Maurer

1 Department of Nuclear Medicine, and 2 Department of Urology, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany

Abbreviations & Acronyms

- 18F-FACBC = anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid
- 18F-FDG = 2-[18F]fluoro-2-deoxy-D-glucose
- BC = bladder carcinoma
- CI = confidence interval
- CT = computed tomography
- EAU = European Association of Urology
- MRI = magnetic resonance imaging
- NA = not applicable
- NPV = negative predictive value
- PC = prostate cancer
- PET = positron-emission tomography
- PPV = positive predictive value
- PSMA = prostate-specific membrane antigen
- RCC = renal cell carcinoma
- SUV = standard uptake value

Abstract: Positron-emission tomography/computed tomography combining both functional and morphological information has emerged as a powerful tool in oncological imaging within the past decades. The most commonly used radiotracer in oncology visualizing metabolic information is 2-[18F]fluoro-2-deoxy-D-glucose. However, the use of 2-[18F]fluoro-2-deoxy-D-glucose in urological oncology is challenging, as it is limited by physiological excretion through the urinary system. Therefore, it is only useful when applied to specific indications in selected patients with urological malignancy; for example, for detection of residual disease in the post-chemotherapy management of patients with seminoma. Despite initial promising results in bladder cancer, no relevant additional diagnostic value with positron-emission tomography using 2-[18F]fluoro-2-deoxy-D-glucose or choline-based tracers could be obtained, and should therefore be used with caution or only within clinical trials. In prostate cancer, however, a paradigm shift in imaging can be observed after development of new tracers that target the prostate-specific membrane antigen. Biochemical recurrent prostate cancer has become a clinically widely accepted indication for prostate-specific membrane antigen ligand positron-emission tomography/computed tomography, with several studies showing superior detection efficacy compared with conventional imaging. For primary high-risk prostate cancer, growing evidence suggests well-improved staging. The present review aimed to provide an overview of the current status of positron-emission tomography imaging in cancer of the urogenital system including the latest advances in 68Ga-labeled and 18F-labeled positron-emission tomography agents targeting the prostate-specific membrane antigen for positron-emission tomography imaging of prostate cancer.

Key words: bladder cancer, kidney cancer, positron-emission tomography, prostate cancer, prostate-specific membrane antigen, testicular cancer.

Introduction

In the past decade, the combination of PET and CT has emerged as an important diagnostic tool in the management of various types of cancer combining both morphological and functional information (for an overview of the most commonly used imaging modalities in oncology, see Table S1). The most commonly used radiotracer in oncology is 18F-FDG, an analog of glucose that is preferentially taken up and trapped inside metabolic hyperactive tumor cells. However, in urological oncology, the use of 18F-FDG is challenging, as it is limited by physiological excretion through the urinary system. Therefore, several new PET tracers are currently under investigation for potential use in urological oncology (Table 1). Within the present article, we aim to review the current and future role of PET/CT in the management of urological malignancies, including testicular, kidney, bladder and PC, discussing both potential indications and limitations.

Testicular cancer

Testicular cancer affected approximately 686 000 people in 2015 globally. It represents 5% of urological tumors, with 3–10 new cases occurring per 100 000 males/per year. 18F-FDG
PET/CT does not have a role in the primary evaluation of a scrotal mass, as the sensitivity of ultrasound to detect testicular tumor is almost 100%. Staging of testicular cancer, especially in patients with seminoma, is a useful indication for 18F-FDG PET/CT, as shown in a recent study by Ambrosini et al. The clinical impact of 18F-FDG PET/CT for staging and restaging of testicular tumors was evaluated including 51 patients with seminoma and 84 patients with non-seminoma. PET/CT showed good sensitivity and specificity for detection of seminoma (92 and 84%, respectively); however, sensitivity was lower for non-seminoma (77 and 95%, respectively). Furthermore, clinical management was influenced in 92% patients with seminoma and in 84% patients with non-seminoma. Another study by Sharma et al. showed the high diagnostic accuracy of 18F-FDG PET/CT for restaging of both seminoma and non-seminoma in 96 patients. 18F-FDG PET/CT showed sensitivity, specificity, PPV, NPV and accuracy of 94.2%, 75.0%, 83.0%, 90.9% and 85.8% overall; 90.0%, 74.0%, 72.0%, 90.9% and 80.8% in seminoma; and 96.8%, 76.9%, 91.1%, 90.9% and 91.1% for non-seminoma, respectively. The difference in PET/CT accuracy for seminoma and non-seminoma was not significant, suggesting the potential usefulness of 18F-FDG PET/CT in all germ cell tumors. However, because of the high diagnostic accuracy of conventional cross-sectional imaging (especially CT) for the primary landing sites of metastatic disease, namely retroperitoneal lymph nodes and lung, 18F-FDG PET/CT currently does not represent first-line imaging in primary staging of testicular cancer. This is in line with the current EAU guidelines on testicular cancer stating that there is no evidence to support the use of 18F-FDG PET in the staging of testis cancer.

Post-chemotherapy residual masses are present in 55–80% of patients with metastatic seminoma. In the current EAU guidelines, 18F-FDG PET/CT plays an increasing role in determining the viability of residual masses of seminoma after chemotherapy, and is recommended in the follow up of patients with any residual mass at least 6 weeks after the end of the last cycle of chemotherapy in order to decide on watchful waiting or active treatment. This is based on data of De Santis et al., who correlated the size of residual tumor in CT (>3 cm or ≤3 cm) with proof of actual vital residual tumor resulting in a sensitivity of 80%, a specificity of 100%, a PPV of 100% and an NPV of 96%, respectively, for 18F-FDG PET/CT. These very promising results were verified in a further study by Becherer et al. There are two systematic reviews and meta-analyses evaluating the diagnostic accuracy of 18F-FDG PET/CT for the prediction of viable residual tumors after chemotherapy in patients with metastatic seminoma. Müller et al. evaluated 130 patients, and showed that 18F-FDG PET/CT was superior to CT for determining tumor size and predicting tumor viability with a sensitivity, specificity, PPV and NPV of 72%, 92% 70 and 93% for PET, and 63%, 59%, 28% and 86% for CT, respectively. Similar results were found by Treglia et al. showing a pooled sensitivity of 78% (95% CI 67–87), a specificity of 86% (95% CI 81–89), a PPV of 58% (95% CI 48–68), an NPV of

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### Table 1: Overview of important PET radiotracers used in urological oncology

| Radiotracer by tumor entity | Biological analog | Target process | Measured effect | Key references |
|-----------------------------|-------------------|----------------|----------------|----------------|
| Testicular tumor            |                   |                |                |
| 18F-FDG                     | Glucose           | Glucose transporters and hexokinases | Aerobic and anaerobic glycolysis, glucose consumption | 3,6,9 |
| Kidney tumor                |                   |                |                |
| 18F-FDG                     | Glucose           | Glucose transporters and hexokinases | Aerobic and anaerobic glycolysis, glucose consumption | 17 |
| 18F-FMISO                   | NA                | Measures hypoxia | Tumor hypoxia | 22 |
| 124I-cG250                  | NA                | Ab-CaIX        | Ab-Ag hypoxia recognizes and joint to CaIX | 23 |
| 11C-acetate                 | Acetate           | Tricarboxylic acid cycle and fatty acid synthase | Lipid synthesis | 20,21 |
| Bladder cancer              |                   |                |                |
| 18F-FDG                     | Glucose           | Glucose transporters and hexokinases | Aerobic and anaerobic glycolysis, glucose consumption | 29,35 |
| 11C-choline                 | Choline           | Choline kinase | Cell membrane metabolism, tumor proliferation | 37-39, 42,43 |
| 11C-acetate                 | Acetate           | Tricarboxylic acid cycle and fatty acid synthase | Lipid synthesis | 55 |
| PC                          |                   |                |                |
| 18F-FDG                     | Glucose           | Glucose transporters and hexokinases | Aerobic and anaerobic glycolysis, glucose consumption | 48,49 |
| 11C-choline/18F-choline      | Choline           | Choline kinase | Cell membrane metabolism, tumor proliferation | 51,53,54 |
| 11C-acetate                 | Acetate           | Tricarboxylic acid cycle and fatty acid synthase | Lipid synthesis | 55 |
| 18F-FACBC                   | Amino-fluorocyclobutane-carboxylic acid | Neutral A–A type amino acid uptake and protein synthesis | Protein synthesis | 56 |
| 68Ga-PSMA                   | PSMA              | Prostate cell surface protein | PSMA-expression on tumor cells | 60,61,63 |
| 18F-PSMA                    |                   |                |                | 75,76,77 |

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94% (95% CI 90–96) and an accuracy of 84% (95% CI 80–88) for 18F-FDG PET/CT. Based on these results, it can be concluded that negative 18F-FDG PET/CT findings of residual masses after chemotherapy in metastatic seminoma warrant follow up, whereas positive findings should lead to subsequent treatment, such as salvage surgery, as mentioned by current guidelines. In order to avoid false positive subsequent treatment, such as salvage surgery, as mentioned, utal masses after chemotherapy in metastatic seminoma war-

to show an enlarged, centrally hypodense lymph node on CT images potentially corresponding to post-therapeutic necrosis. However, corresponding (b) axial 18F-FDG PET and (c) fused 18F-FDG PET/CT show an intense, focal uptake corresponding to residual vital tumor tissue.

Fig. 1 18F-FDG PET/CT in a 42-year-old patient with seminoma and retroperitoneal lymph node metastases. (a) Restaging 3 months after adjuvant chemotherapy shows an enlarged, centrally hypodense lymph node on CT images potentially corresponding to post-therapeutic necrosis. However, corresponding (b) axial 18F-FDG PET and (c) fused 18F-FDG PET/CT show an intense, focal uptake corresponding to residual vital tumor tissue.

Kidney cancer

RCC is the most common malignant kidney tumor, with an estimated 62 700 new cases in 2016 in the USA. CT is the primary imaging modality for diagnosis, staging and treatment planning of RCC. PET-based imaging modalities do not play a major role in local diagnosis of RCC, as most of the radiotracers, such as 18F-FDG, are eliminated by the kidneys, leading to significant background activity that prevents accurate diagnosis. Even application of diuretics or delayed imaging could not overcome this limitation so far. Furthermore, renal parenchyma shows high 18F-FDG uptake itself, so differentiation to malignant lesions is difficult. If 18F-FDG-PET is carried out in the diagnosis of RCC, the maximum SUV

varies between <1.5 and >2.13,14 Thus, no specific cut-off SUV could be determined, and no correlation between SUV values and different subtypes of RCC could be determined.15

In contrast, 18F-FDG-PET has a higher sensitivity in metastatic RCC, and shows increased uptake in 95% of the metastases detected by CT. A representative example can be seen in Figure 2. The role of 18F-FDG-PET in RCC was evaluated in a meta-analysis by Wang et al. Pooled sensitivity and specificity for detection of renal lesions with 18F-FDG-PET was 62% and 88%, and 79% and 90% for the detection of extrarenal lesions, respectively. The use of hybrid PET/CT scanners could increase sensitivity to 91% and specificity to 88% with consistent results.17 However, most of the studies included in their meta-analysis were PET examinations without CT. Therefore, combined PET/CT might achieve higher sensitivity and specificity. Interestingly, in a study by Alongi et al., 18F-FDG PET influenced therapeutic strategy in 43% of patients with RCC despite moderate sensitivity and specificity of 74% and 80%, respectively.18 Furthermore, patients with FDG-positive lesions presented with a significantly lower 5-year overall survival rate compared with those without FDG-avid lesions (69% vs 19%, respectively). In patients with metastatic RCC, high SUVmax values in 18F-FDG-PET correlate with a poor prognosis and a limited overall survival.13,14 However, RCC can present with limited FDG uptake, most likely due to the dominant incidence of the clear cell subtype of the disease. There is emerging evidence that the rarer papillary variant of RCC might have avidity for FDG.19 Therefore, there is growing interest in non-FDG molecular PET imaging agents. Various tumor targets have been evaluated, including hypoxia (18F-FMISO), aerobic metabolism (11C-acetate), malignant cell proliferation (18F-FLT) or amino acid transport (11C-methionine). For example, 11C-acetate was studied for RCC by Shreve et al. and Kotzerke et al. with contradictory results. 18F-FMISO has been evaluated for staging of RCC by Lawrentschuk et al., reporting mild uptake in seven out of 11 primary tumors. Furthermore, the antibody, cG250 (girentuximab), has been studied as it binds to carbonic anhydrase 9, which is overexpressed in clear cell RCC. In a phase III study, 124I-cG250 PET/CT showed a sensitivity of 86.2% and a specificity of 85.9% for the diagnosis of clear cell RCC.23 Altogether, so far none of these radiotracers could be established in the clinical routine. Thus, PET imaging in RCC remains an area of

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conventional cross-sectional imaging methods, such as MRI. Resolution (spatial) could be observed due to superior spatial resolution of assessment of metastatic lesions and disease recurrence. Here, 96%.27,28 Furthermore, no additional benefit of forced diuresis with sensitivities ranging from 85% to 84.0%, respectively.26 Several methods have been proposed to overcome interference from radioactivity in urine, including early imaging, late imaging after voiding, dual phase imaging, bladder catheterization or irrigation and forced diuresis with sensitivities ranging from 85% to 96%.27,28 Furthermore, no additional benefit of PET in local staging (e.g. visualization of depth of bladder wall infiltration) could be observed due to superior spatial resolution of conventional cross-sectional imaging methods, such as MRI.

The most widely accepted indication for PET in BC is assessment of metastatic lesions and disease recurrence. Here, 18F-FDG is the radiotracer for which the most experience exists. The largest study published to date evaluated 18F-FDG PET in the preoperative staging of BC in 233 patients compared with histopathology after radical cystectomy or follow-up imaging. Sensitivity for pelvic lymph node involvement increased from 45% to 69% with 18F-FDG PET/CT in comparison with CT alone, with almost similar specificity of 98% and 95%, respectively. The PET scan was able to detect metastatic disease outside of the pelvis with a sensitivity of 54% compared with 41% for the staging CT, with similar specificities of 97% and 98%. Although combined PET/CT provides a small improvement in preoperative staging of BC, the authors concluded that the advantage is not significant enough to justify the additional cost.29 These results are concordant with the results of Jeong et al. and Swinnen et al., who evaluated the diagnostic accuracy of 18F-FDG PET/CT for lymph node staging of BC patients undergoing radical cystectomy with extended pelvic lymphadenectomy compared with conventional CT in 61 and 51 patients. On both patient and lymph node template-based analysis, no additional benefit of 18F-FDG PET compared with CT alone could be observed that would justify the additional cost of a PET examination.30,31 However, some studies reported significantly improved detection rates regarding the detection of lymph node metastases with 18F-FDG PET. Hitier et al. reported on increasing sensitivity from 9% to 36% in 52 patients, with almost the same specificity of 87% and 90%, respectively. Therefore, patient selection for 18F-FDG PET examination based on risk factors for development of lymph node metastases might seem justified.32 This approach was followed by Kollberg et al., who evaluated patients with only high-risk muscle-invasive BC defined as stage T3/T4 disease or as stage T2 with hydronephrosis or high-risk histological features. Compared with CT alone, 18F-FDG PET/CT provided more findings suggesting malignant manifestations in 48 out of 103 patients (47%). This changed further treatment in 27% of patients. In 16 patients, the detection of disseminated BC resulted in cancellation of the initially intended cystectomy, and in 12 patients the identification of disseminated disease resulted in inductive chemotherapy before radical cystectomy.33 In a study of Mertens et al., these results could be confirmed with a change in treatment in almost 20% of the 96 patients studied.34 In a further study of Mertens et al. including 211 patients with muscle-invasive BC, the presence of extravesical FDG-avid lesions on PET/CT was identified as an independent prognostic indicator of mortality (hazard ratio 3.0, 95% CI 1.7–5.1),35 confirming already published results.36

Similar results for staging of BC have been reported for the radiotracer 11C-choline. Figures 3 and 4 show two representative 11C-choline PET/CT examinations in a patient with primary and recurrent BC, respectively. Primary staging of lymph node metastases in 26 patients and restaging in 25 patients resulted in an improved sensitivity in comparison with CT alone.37,38 In contrast, in a study by the present

**Fig. 2** Staging examination with 18F-FDG PET/CT in a 57-year-old patient with known RCC. CT images show (a) an enlarged para-aortic lymph node (axial diameter 9 mm) with corresponding focal FDG uptake on (b) PET and (c) fused PET/CT images highly suspicious for singular lymph node metastasis.

**Bladder carcinoma**

BC is the ninth most common cancer worldwide and the most frequent type of cancer of the urinary tract. More than 90% of BCs are urothelial (transitional cell) carcinomas. At diagnosis, approximately 70% of patients have superficial tumors that tend to recur, whereas 30% of patients present with a muscle-invasive BC and a high chance of early systemic dissemination.25 After initial promising results of PET in the diagnostic work-up in BC, its limitations recently became more evident. The standard method of diagnosing BC remains cystoscopy, including biopsy/resection with histopathological evaluation. PET is not used routinely for the standard method of diagnosing BC remains cystoscopy, including biopsy/resection with histopathological evaluation. PET is not used routinely for the diagnosis, approximately 70% of patients have superficial tumors that tend to recur, whereas 30% of patients present with a muscle-invasive BC and a high chance of early systemic dissemination.25 After initial promising results of PET in the diagnostic work-up in BC, its limitations recently became more evident. The standard method of diagnosing BC remains cystoscopy, including biopsy/resection with histopathological evaluation. PET is not used routinely for the diagnosis, approximately 70% of patients have superficial tumors that tend to recur, whereas 30% of patients present with a muscle-invasive BC and a high chance of early systemic dissemination.25 After initial promising results of PET in the diagnostic work-up in BC, its limitations recently became more evident. The standard method of diagnosing BC remains cystoscopy, including biopsy/resection with histopathological evaluation. PET is not used routinely for the diagnosis, approximately 70% of patients have superficial tumors that tend to recur, whereas 30% of patients present with a muscle-invasive BC and a high chance of early systemic dissemination.25 After initial promising results of PET in the diagnostic work-up in BC, its limitations recently became more evident. The standard method of diagnosing BC remains cystoscopy, including biopsy/resection with histopathological evaluation. PET is not used routinely for the
authors comprising 44 patients with BC before radical cystectomy, those positive results regarding lymph node staging could not be reproduced.39 Both patient and field-based evaluation compared with histopathological evaluation showed no substantial difference between 11C-choline PET/CT and CT alone. Regarding the prognostic value of 11C-choline PET/CT and CT for predicting survival, no additional benefit with 11C-choline PET/CT in comparison with CT alone was observed in this cohort.40 However, this might be attributable to the low patient numbers published so far and in the inclusion of not only high-risk BC patients. Interestingly, no superiority was observed in a study comparing 11C-choline PET and 18F-FDG PET in 20 patients with BC. Therefore, both radiotracers might be regarded most probably as equivalent.41 Another radiotracer used in BC is 11C-acetate. However, only one study evaluating 11C-acetate PET/CT in the staging of BC and one study comparing 11C-acetate with 11C-choline in 14 patients have been published so far suggesting almost equivalence.42,43 Altogether, it has to be admitted that PET in BC represents no standard imaging technique. Furthermore, according to the EAU guidelines, there are currently insufficient data on the use of 18F-FDG PET/CT in bladder cancer, allowing for no recommendation.44 However, in patients with muscle-invasive BC and a high-risk profile, PET might be of additional diagnostic and prognostic value, with 18F-FDG being the radiotracer studied most intensively. More BC-specific radiotracers, however, would be desirable.

Prostate cancer

PC is the most common cancer in men and the third most common cause for cancer-related death worldwide.45 Therefore, molecular PC imaging methods have increasingly been used within the past decade and are currently an area of intense research. Staging of primary PC is crucial for further treatment planning and prognosis. However, cross-sectional imaging has been shown to be limited for N-staging related to the presence of nodal metastases in normal-sized lymph nodes as well (pooled sensitivity and specificity of 42% and 82% for CT, and 39% and 82% for MRI, respectively).46,47 In the setting of biochemical recurrence, accurate localization of recurrence and the extent of disease are of utmost importance to tailor potential salvage therapy. Apart from multi-parametric MRI for the detection of local recurrence, conventional imaging is rarely carried out due to its inability to clearly identify the site of recurrence.

From 18F-FDG to 11C-choline

The most common commercially available radiotracer in oncology is 18F-FDG. However, 18F-FDG PET is of limited value for detection and localization of primary PC and initial staging of disease, as only aggressive, poorly differentiated or undifferentiated PC shows a high glycolytic rate.45-49 In Europe, radiolabeled choline derivatives (18F-choline or
The use of PSMA as a target for PC imaging has recently revolutionized PC imaging and is an area of intense ongoing research. PSMA is a cell-surface protein that is highly overexpressed on PC cells, and its expression increases with tumor aggressiveness, metastatic disease and disease recurrence. The most widely used and studied 68Ga-labeled PSMA ligands for PET-imaging are 68Ga-PSMA HBED-CC (68Ga-PSMA-11) followed by 68Ga-PSMA-617 and 68Ga-PSMA-I&T. Currently, imaging of biochemical recurrence is the clinically most accepted and validated indication for PSMA ligand PET/CT. A representative example of 68Ga-PSMA-11 PET/CT in a patient with early biochemical recurrence is shown in Figure 5. Several mainly retrospective studies on the value of 68Ga-PSMA ligand PET/CT in restaging of PC show a higher diagnostic efficacy compared with choline derivatives.57–59 Afshar-Oromieh et al. showed that SUVmax and tumor : background ratios were superior for 68-Ga-PSMA-11 compared with 18F-choline.57 Schwenck et al. reported a higher detection rate of 68Ga-PSMA-11 PET/CT than 11C-choline PET/CT for lymph node metastases and bone metastases.59 Two large retrospective studies of 319 and 248 patients showed detection rates for 68Ga-PSMA-11 PET/CT in biochemical recurrence of 80–90%.60,61 Concordant results were found in a recently published study by Afshar-Oromieh et al. on 1007 patients with biochemical recurrence and a detection rate of 79.5%.62 In patients after curative treatment with PSA levels <0.5 ng/mL, the reported detection rate of PSMA ligand PET/CT ranged from 46% to 58% in different studies.58,60,61 Recently, a systematic review by Perera et al. pooling 10 different studies showed a predicted positive rate of PSMA ligand PET of 42%, 58%, 76% and 95% for PSA values of 0–0.2, 0.2–1, 1–2 and >2 ng/mL, respectively.63 A recently published study by the present authors of 272 patients with early biochemical recurrence after radical prostatectomy showed similar results, with PSMA-positive lesions detected in 74 out of 134 patients (55%, 95% CI 46–64) with a PSA value of 0.2–0.5 ng/mL, and in 102 out of 138 patients (74%, 95% CI 66–81) with a PSA value >0.5–1.0 ng/mL.64 The main sites of recurrence were pelvic or retroperitoneal lymph nodes metastases, followed by local recurrence. In a multivariable logistic regression model, concurrent androgen deprivation therapy and PSA values were identified as the most relevant predictors of positive 68Ga-PSMA-11 PET. Another study by the present authors evaluated the value of 68Ga-PSMA-11 PET/CT for the assessment of lymph node metastases in PC patients with biochemical recurrence (median PSA 1.31 ng/mL; interquartile range 0.75–2.55 ng/mL) in comparison with histopathology after salvage lymphadenectomy.65 The specificity of 68Ga-PSMA-11 PET and morphological imaging was 97.3% and 99.1%, respectively. The high specificity of morphological imaging is most likely explained by the use of very strict criteria for morphological assessment of lymph node metastases with a short axis diameter of >10 mm for rating as tumor manifestation. However, 68Ga-PSMA-11 PET was shown to be significantly superior to morphological imaging in...
detection of lymph node metastases, with a detection rate of 77.9% for $^{68}$Ga-PSMA ligand PET (53/68 histopathologically proven metastatic lymph node fields) and 26.9% for morphological imaging (positive in just 18/67 lymph node fields).

For staging of primary PC, there is growing evidence that underlines the value of PSMA ligand PET/CT as well. Several studies showed a clear superiority of PSMA ligand PET/CT compared with conventional imaging, especially for N- and M-staging in high-risk PC patients.$^{66-70}$ In a retrospective study by the present authors including 130 patients with primary intermediate- to high-risk PC $^{68}$Ga-PSMA-11, PET was shown to be significantly superior to morphological imaging for N-staging both on a patient and template base ($P = 0.002$ and $P < 0.001$, respectively). On a patient basis, sensitivity, specificity and accuracy were 65.5%, 98.9% and 88.5% for $^{68}$Ga-PSMA-11 PET, and 43.9%, 85.4% and 72.3% for morphological imaging, respectively.$^{68}$ Similar results on the diagnostic efficacy of PSMA ligand PET for the detection of lymph node metastases were obtained in other studies as well.$^{67,70}$ Furthermore, $^{68}$Ga-PSMA-11 PET significantly outperforms bone scan for detection of bone metastases because of its high sensitivity and specificity on both patient- and region-based analysis ($P = 0.006$ and $P < 0.0001$, respectively).$^{69}$ For localization of primary PC lesions combined, $^{68}$Ga-PSMA PET/MRI was evaluated in 53 intermediate-/high-risk patients before radical prostatectomy. Here, $^{68}$Ga-PSMA PET/MRI significantly outperformed multiparametric MRI or $^{68}$Ga-PSMA PET with a sensitivity and specificity for tumor localization on a sextant base of 76% and 97% (58% and 82% for multiparametric MRI, 64% and 94% for $^{68}$Ga-PSMA PET, respectively).$^{71}$ Furthermore, several studies assessing intraprostatic tumor localization in correlation to histopathology by $^{68}$Ga-PSMA PET/CT showed significantly higher $^{68}$Ga-PSMA uptake in positive segments compared with negative segments ($\text{SUV}_{\text{max}}$ 11.8 vs 4.9 and 11.0 vs 2.7, respectively, $P < 0.001$ each).$^{72-74}$

18$^F$-labeled PSMA ligand PET

Recently, 18$^F$-labeled compounds have been developed and are used for PSMA-based PET imaging, such as 18$^F$-DCFBC, 18$^F$-DCFPyL and 18$^F$-PSMA-1007.$^{75-77}$ Apart from a longer half-life of 18$^F$ compared with $^{68}$Ga (110 vs 68 min) allowing distribution to other sites, it is logistically appealing due to the possibility of central radionuclide production in cyclotron producing large-scale batches. Further potential advantages are higher image quality due to lower positron-emission energy of 18$^F$ (0.65 vs 1.9 MeV for $^{68}$Ga). However, phantom measurements in human scanners found comparable results for both nuclides.$^{78}$ So far, published experience with 18$^F$-labeled PSMA ligands is limited, and includes only a small number of patients studied. In metastatic PC patients, diagnostic performance of 18$^F$-DCFBC, as well as 18$^F$-DCFPyL PET/CT, was shown to be superior compared with conventional imaging.$^{79,80}$ Furthermore, in a head-to-head comparison, 18$^F$-DCFPyL PET/CT performed equally well compared with $^{68}$Ga-PSMA-11 PET/CT in 14 patients.$^{81}$ A follow-up study from Dietlein et al. using PSA-adjusted parallel biochemically recurrent PC patient cohorts including 191 patients found that 18$^F$-DCFPyL was non-inferior to $^{68}$Ga-PSMA-11, and suggested an improved sensitivity of the 18$^F$-labeled radiotracer in the PSA range of 0.5–3.5 ng/mL.$^{82}$ In the first study evaluating the use of 18$^F$-DCFBC PET/CT in 13 patients with primary PC, sensitivity of MRI was superior to 18$^F$-DCFBC PET/CT. However, 18$^F$-DCFBC PET/CT showed a higher specificity.$^{76}$ The first retrospective study using 18$^F$-PSMA-1007 in eight patients with primary PC suggests its high diagnostic potential by correctly detecting 18 of 19 histopathologically validated lymph node metastases.$^{77}$ Figure 6 shows a representative 18$^F$-PSMA-1007 PET/MR in a patient with primary PC. In a recently published study by Giesel et al., 18$^F$-PSMA-1007-positive lesions were detected in nine of 12 patients (75%) with biochemical recurrence (median PSA 0.60 ng/mL; range 0.08–6.50 ng/mL).$^{83}$ 18$^F$-PSMA-1007 PET/CT was unable to detect any tumor-suggestive lesions in three patients. However, all of them presented with PSA values of <0.5 ng/mL. A specific advantage of 18$^F$-PSMA-1007 for the detection of local recurrence might be its low urinary clearance facilitating the evaluation of lesions close to the urinary tract.

In summary, so far, EAU guidelines suggest no role of PET in staging of PC because of the limited evidence;
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However, PET/CT using choline or PSMA in recurrent disease is recommended in patients with PSA >1 ng/mL after radical prostatectomy. Furthermore, choline PET/CT imaging is recommended after primary radiation therapy to rule out lymph nodes or distant metastases in patients fit enough for curative salvage treatment. 

**Conclusion**

In oncology, the use of PET/CT with 18F-FDG, the most commonly used radiotracer, is constantly increasing. Although 18F-FDG in urological oncology is challenging due to urinary excretion of FDG, 18F-FDG PET/CT was recently shown to be useful in selected indications; for example, therapy monitoring of seminoma. The rapid development of new radiotracers together with technological advances further improves the visualization of urological malignancies. A paradigm shift can be observed, especially in PC imaging. PSMA-based PET/CT has become a clinically accepted method providing high diagnostic efficacy in recurrent PC, as well as in staging of high-risk primary PC. There is increasing evidence that PSMA ligand PET/CT influences treatment decisions by the detection and localization of recurrent disease that is often missed by using conventional imaging methods.

**Conflict of interest**

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

Table S1. Overview of the most commonly used oncological imaging modalities in nuclear medicine and radiology.