Targeting PSMA by radioligands in non-prostate disease—current status and future perspectives

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Abstract
Background Prostate-specific membrane antigen (PSMA) is the up-and-coming target for molecular imaging of prostate cancer. Despite its name, non-prostate-related PSMA expression in physiologic tissue as well as in benign and malignant disease has been reported in various publications. Unlike in prostate cancer, PSMA expression is only rarely observed in non-prostate tumor cells. Instead, expression occurs in endothelial cells of tumor-associated neovasculature, although no endothelial expression is observed under physiologic conditions. The resulting potential for tumor staging in non-prostate malignant tumors has been demonstrated in first patient studies. This review summarizes the first clinical studies and deduces future perspectives in staging, molecular characterization, and PSMA-targeted radionuclide therapy based on histopathologic examinations of PSMA expression.

Conclusions The non-exclusivity of PSMA in prostate cancer opens a window to utilize the spectrum of available radioactive PSMA ligands for imaging and molecular characterization and maybe even therapy of non-prostate disease.

Keywords Prostate cancer · PSMA · Prostate-specific membrane antigen · Endothelium · PET/CT · Angiogenesis

Introduction
The prostate-specific membrane antigen (PSMA, also known as glutamate carboxypeptidase II, N-acetyl-L-aspartyl-l-glutamate peptidase I, and folate hydrolase 1) is a type II transmembrane protein physiologically expressed by prostate tissue and significantly overexpressed by most prostate cancer (PCA) cells [1]. Interestingly, studies have shown increasing PSMA expression with higher tumor stage and grade [2]. The recent development of specific PSMA-targeted small molecule ligands allows this trait of PCA cells to be exploited for clinical positron emission tomographic (PET) imaging of PCA [3, 4].

Noteworthy, PSMA ligands are characteristically internalized into the cell upon binding, resulting in intracellular buildup and high levels of accumulation even in small metastases [5]. Currently, the most widely used PSMA ligand is 68Ga-PSMA-11 (also known as 68Ga-PSMA-HBED-CC) introduced in 2012, initiating a widespread clinical use of PSMA ligands for PET imaging. A variant of this PSMA ligand, PSMA-617, can also be labeled with 68Ga for PET imaging but is especially used in PSMA-targeted radioligand therapy [6]. Meanwhile, promising 18F-labeled ligands have been introduced, 18F-DCFPyL [7], and 18F-PSMA-1007 [8], which show favorable characteristics in terms of lesion detection [9, 10] and tracer metabolism [11]. Moreover, first 99mTc-labeled PSMA-targeted variants are currently being evaluated [12].

Now, supported by an ever-growing number of publications, PET imaging with PSMA ligands is the emerging new reference standard for imaging of prostate cancer, particularly concerning staging of lymph node (N) and distant (M) metastases [13–15]. A retrospective study including 130 patients with PCA scheduled for radical prostatectomy...
could show significantly superior diagnostic efficacy of $^{68}$Ga-PSMA-PET/CT for lymph node staging compared to CT or MRI [16]. Concerning the detection of bone metastases $^{68}$Ga-PSMA-PET/CT was shown to outperform planar bone scintigraphy in a study comprising 126 patients receiving both examinations. Furthermore, the results indicate that bone scintigraphy rarely offered any additional information to PSMA-PET/CT [17]. Compared to PET/CT imaging with the former reference standard - radiolabeled choline - significantly higher detection rates, SUV$_{\text{max}}$ values, and tumor-to-background ratios could be shown for $^{68}$Ga-PSMA-11 [18, 19].

However, unlike originally thought in 1987 and reflected in the denomination "prostate-specific membrane antigen" [20], PSMA is not solely expressed by prostate tissue [21, 22]. PSMA is also physiologically expressed by other tissues such as the small intestine, renal tubules, salivary glands, and astrocytes. Correspondingly, the physiologic tracer distribution seen in PET should be known to the clinicians reading PSMA studies. Two studies evaluating the physiological biodistribution of $^{68}$Ga-PMSA-11 in 37 and 55 patients showed intense tracer uptake in both kidneys and salivary glands. Moderate uptake is seen in lacrimal glands, liver, spleen, in the small bowel, large bowel, and the rectum [4]. In 22% of the patients, $^{68}$Ga-PSMA-11 uptake was seen in the thyroid gland and 21% displayed uptake in the synovia of the knee [23]. Since $^{68}$Ga-PSMA-11 is mainly excreted via the kidneys, intense tracer accumulation is seen in the bladder and in transit in the ureters. Consequently, differentiating between paraaortic lymph node metastases and ureter retention is a common challenge in clinical routine [24]. As could be shown by Freitag et al., radiotracer accumulation in the bladder can hinder the detection of local recurrence after radical prostatectomy [25].

Importantly, PSMA overexpression also occurs in pathophysiologic processes other than PCA, especially in the neovascularature of multiple malignancies [2]. This has important implications for PSMA-targeted imaging and possibly also therapies. Lately, there have been an increasing number of reports concerning radionuclide accumulation in benign and malignant lesions other than PCA. They represent important pitfalls in the clinical use of PSMA-PET. These were comprehensively summarized in a recent review [26].

The aim of this review is to give an overview on the potential of PSMA-targeted imaging in diseases other than PCA. We not only summarize the existing clinical data but also deduce the potential of radioactive PSMA ligands for staging, molecular characterization, and potentially even therapy for non-prostate malignant disease based on histopathological data concerning PSMA expression in various pathologies.

### Review criteria

A literature review of PubMed/Medline was performed using the following sets of keywords: (1) ("PSMA" or "carboxypeptidase") AND ("PET" or "positron"). (2) ("vascular" or "neoangiogenesis" or "neovascularature") AND "PSMA". The search included articles published online through August 31, 2017. The two keyword sets yielded 522 and 147 publications, respectively. After excluding publications that primarily focused on PCA, the remaining publications were reviewed and discussed in the article if suitable.

### PSMA imaging for staging of other malignant tumors

Today PET imaging in staging and re-staging has an important role in various malignant processes. So far, PSMA-PET is routinely performed only in specialized centers as part of staging and re-staging of PCA. Although only few other tumors express PSMA on the cell surface, PMSA expression in the endothelium of tumor-associated newly formed vessels is very common in various malignancies and also in vessels involved in benign processes [27]. To bear a potential for PSMA imaging in staging of malignancy, consistent and strong PSMA expression is self-evidently the most important prerequisite. The considerable variation amongst different malignant tumor entities (Table 1) in respect to PSMA expression is documented by an extensive body of histopathological publications. Unfortunately, remarkable discrepancies exist between publications that focus on this issue. As an example, the rate of PSMA expression in the neovascularature of transitional cell carcinomas of the bladder is reported with 41/94 [47], 96/96 [135], 3/3 [142], 7/13 [1], and 6/6 [27] and in referring tumor cells with 3/96 [135], 0/13 [1], 59/346 [144], and 0/6 [27]. Moreover, PSMA positivity in normal urothelium ranged between 0/846 [144], 0/5 [27], 18/18 [22] and 9/9 [145]. These discrepancies are most likely explained by the different techniques used for expression verification (different antibodies, microarray techniques, qPCR), quantification (staining strength, proportion of positive cells) and respective cut-offs for classification. Although the published results ex vivo are more consistent for most other tumor entities, it should be emphasized that ex vivo analyses only allow a rough estimate of PSMA positivity, especially as no absolute quantification of PSMA expression is available for immunohistochemistry, therefore precluding a direct correlation to target availability for PET imaging.

Amongst non-PCA diseases studied by PSMA-PET, clear cell renal cell carcinoma (ccRCC) is by far the most abundant entity as several aspects underline a high potential for PSMA imaging: (1) ccRCC is a heavily vascularized tumor and histopathologic studies consistently reported high PSMA
Table 1  Overview of reports of PSMA expression in non-prostatic tissue

<table>
<thead>
<tr>
<th>Tissue origin</th>
<th>Classification</th>
<th>No. of reported PSMA-PET cases (rate of PSMA positivity is given when deducible)</th>
<th>No. of reported cases with histology (rate of PSMA positivity is given when deducible)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal gland</td>
<td>Adrenocortical carcinoma</td>
<td>1 [28]</td>
<td>15/15 [28]</td>
</tr>
<tr>
<td></td>
<td>Adrenocortical adenoma</td>
<td>2 [29, 30]</td>
<td>2/16 [28]</td>
</tr>
<tr>
<td>Bone</td>
<td>Osteosarcoma</td>
<td>1 [31]</td>
<td>21/45 [32]</td>
</tr>
<tr>
<td></td>
<td>Ewing sarcoma</td>
<td>1/4/106 [33]</td>
<td>1/38</td>
</tr>
<tr>
<td></td>
<td>Paget’s disease</td>
<td>8 [34–41]</td>
<td>0/12 [32]</td>
</tr>
<tr>
<td></td>
<td>Fibrous dysplasia</td>
<td>3 [23, 31, 42]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Osteofibrous dysplasia</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Fracture</td>
<td>2 [43, 44]</td>
<td></td>
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<tr>
<td></td>
<td>Osteoarthritis</td>
<td>7 [23]</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>Breast cancer</td>
<td>1 [45]; 16/19 (mean SUVmean local 2.45, SD 2.55; distant metastases 6.86, SD 5.68; lymph node metastases 3.18, SD 1.79) [46]</td>
<td>30/44 [47], 82/106 [48], 5/6 [27]</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Pseudoangiomatous stromal hyperplasia</td>
<td>1 [49]</td>
<td></td>
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<tr>
<td></td>
<td>Meningioma</td>
<td>3 [50–52]; 1/1 [53]</td>
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<tr>
<td></td>
<td>Glioma</td>
<td>1/1 [54], 5/5 (SUVmax 5.8–21.7) [53], 1/1 [54], 1/1 [27], 32/32 [56], 3/3 [55]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Central nervous system lymphoma</td>
<td>2/2 [53]</td>
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<tr>
<td></td>
<td>Stroke</td>
<td>2 [57, 58]</td>
<td></td>
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<tr>
<td>Eye</td>
<td>Physiologic in astrocytes</td>
<td></td>
<td>[59]</td>
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<tr>
<td></td>
<td>Choroidal neovascular membrane</td>
<td></td>
<td>0/30 [60]</td>
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<tr>
<td>Female reproductive system</td>
<td>Ovary cancer</td>
<td>27/34 [47], 31/31 [61]</td>
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<tr>
<td></td>
<td>Endometrial carcinoma</td>
<td>23/23 [61]</td>
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<tr>
<td></td>
<td>Vulvar carcinoma</td>
<td>5/20 [61]</td>
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<td></td>
<td>Cervical carcinoma</td>
<td>4/8 [61]</td>
<td></td>
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<tr>
<td>Head and neck</td>
<td>Squamous cell carcinoma</td>
<td>2 [62], [50]</td>
<td>72/96 [63]</td>
</tr>
<tr>
<td>Intestines</td>
<td>Colorectal adenocarcinoma</td>
<td>3 [64–66]</td>
<td>75/100 [67], 130/154 [68], 3/19 [1], 5/5 [27]</td>
</tr>
<tr>
<td>Kidney</td>
<td>Clear cell renal cell carcinoma</td>
<td>8 [69–76]; 8/8 (SUVmax local 3.7–36.5; metastases 1.5–48) [77], 5/5 (SUVmax 1.6–19.3) [78], 6/7 (SUVmax 5.3–26.5) [79], 4/4 (SUVmax local 1.7–27.2; metastases 3.4–25.6) [80]</td>
<td>2 [70, 71], 11/11 [27], 15–20/20 [81], 16/21 [82], 29/30 [83], 37/38 [47], 188/228 [84]</td>
</tr>
<tr>
<td></td>
<td>Papillary renal cell carcinoma</td>
<td>1/1 [77], 0/1 [79], 1/1 [80]</td>
<td>0/20 [82], 11/15 [83], 3/22 [84]</td>
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<tr>
<td></td>
<td>Chromophobe renal cell carcinoma</td>
<td></td>
<td>5/16 [82], 13/15 [83], 3/7 [84]</td>
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<tr>
<td></td>
<td>Oncocytoma</td>
<td>10/19 [82]</td>
<td>14/15 [83]</td>
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<tr>
<td></td>
<td>Angiomyolipoma</td>
<td>0/19 [82]</td>
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<tr>
<td></td>
<td>Transitional cell carcinoma</td>
<td>3/14 [82]</td>
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<tr>
<td></td>
<td>Not specified carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Physiologic in luminal proximal tubule cells</td>
<td>1 [85]</td>
<td>8/17 [1]</td>
</tr>
<tr>
<td>Liver</td>
<td>Hepatocellular carcinoma</td>
<td>3 [86–88]</td>
<td>38/42 [47]</td>
</tr>
<tr>
<td></td>
<td>Cholangiocarcinoma</td>
<td></td>
<td>2/4 [47]</td>
</tr>
<tr>
<td>Lung</td>
<td>Non-small-cell lung carcinoma</td>
<td>2 [50, 89]; 7/7 (mean SUVmax 5.5, SD 1.9) [90]</td>
<td>7/7 [90], 74/87 [91], 5/5 [27]</td>
</tr>
<tr>
<td></td>
<td>Small-cell lung carcinoma</td>
<td></td>
<td>21/30 [91]</td>
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<tr>
<td></td>
<td>Mesothelioma</td>
<td></td>
<td>9/36 [47]</td>
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<tr>
<td></td>
<td>Opacities and bronchiectasis</td>
<td>1 [92]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sarcoïdosis in hilar lymph nodes</td>
<td>2 [93, 94]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Activated tuberculosis</td>
<td>1 [90]</td>
<td>2/2 [90]</td>
</tr>
<tr>
<td></td>
<td>Anthracosis</td>
<td>1 [95]</td>
<td></td>
</tr>
<tr>
<td>Lymphatic</td>
<td>Lymphoma</td>
<td>3 [50, 96, 97]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple myeloma</td>
<td>2 [98, 99]</td>
<td></td>
</tr>
<tr>
<td>Male reproductive system</td>
<td>Penis squamous cell carcinoma</td>
<td>1 [100]</td>
<td></td>
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<tr>
<td></td>
<td>Testicular embryonal carcinoma</td>
<td></td>
<td>1 [100]</td>
</tr>
<tr>
<td></td>
<td>Amyloidosis of seminal vesicles</td>
<td>1 [101]</td>
<td>1/1 [27]</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Pancreatic adenocarcinoma</td>
<td></td>
<td>124/147 [102], 4/4 [27]</td>
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<tr>
<td></td>
<td>Serous cystadenoma</td>
<td>1 [103]</td>
<td></td>
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<tr>
<td></td>
<td>Neuroendocrine tumor</td>
<td>1 [104]</td>
<td></td>
</tr>
</tbody>
</table>
expression rates (75–97%) in tumor-associated neovascularity [47, 81–84]. (2) Reliable and exact lesion detection could have a high impact on therapeutic strategies, as surgical and radio ablative approaches are frequently employed in oligometastatic ccRCC in order to enhance local control and survival [146]. Overall, findings in 32 patients with histopathologically proven ccRCC have been published of which eight are reported in single case reports [69–76] and 24 were included in four studies with multiple patients [77–80]. PSMA-PET tracer uptake in any tumor site was observed in 23 of these 24 patients. Rhee et al. compared ⁶⁸Ga-PSMA-11 PET/CT imaging to diagnostic CT imaging in ten patients of whom eight had proven ccRCC and found a higher sensitivity of PSMA-PET/CT (92 vs. 69%) and a higher positive predictive value (97 vs. 80%) compared to CT based on correlation with histopathologic investigation of 36 tumor sites. Most importantly, PSMA-PET/CT led to a change in the therapeutic strategy in two patients through better delineation of the extent of an intravenous tumor thrombus and detection of an additional intrahepatic metastasis, respectively [77]. In good agreement, Rowe et al. published a superior sensitivity (95 vs. 79%) of ¹⁸F-DCFPyL-PET/CT compared to conventional imaging (CT or MRI) in five patients [78]. The lack of histopathologic investigation of detected sites and resulting uncertainty of specificity in this study was compensated by a single patient rapid autopsy study where PSMA

<table>
<thead>
<tr>
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<th>No. of reported PSMA-PET cases (rate of PSMA positivity is given when deducible)</th>
<th>No. of reported cases with histology (rate of PSMA positivity is given when deducible)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral nervous system</td>
<td>Schwannoma</td>
<td>2 [105, 106]</td>
<td>3/14 [33], 11/11 [107]</td>
</tr>
<tr>
<td></td>
<td>Other nerve sheath tumors</td>
<td>1 [108]</td>
<td>7/25 [33]</td>
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<tr>
<td></td>
<td>Traumatic neuroma</td>
<td>1 negative [109]</td>
<td>1 negative [109]</td>
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<tr>
<td></td>
<td>Physiologic in ganglia</td>
<td>cervicothoracic 3 [110]; 76/85 celiac (SUV&lt;sub&gt;max&lt;/sub&gt; 1.57–6.38) [111]; at least one positive ganglion 94/100 (SUV&lt;sub&gt;max&lt;/sub&gt; 1.2–6.5) [112]</td>
<td>1 [111]</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>Adenoid cystic carcinoma</td>
<td>2 [113, 114]; 9/9 (median SUV&lt;sub&gt;max&lt;/sub&gt; local 2.52, IQR 2.41–5.95; metastases 4.01, IQR 2.66–8.71) [115]</td>
<td>1 [114]; 6/6 [115]</td>
</tr>
<tr>
<td></td>
<td>Physiologic in acinar epithelium</td>
<td></td>
<td>[116]</td>
</tr>
<tr>
<td>Skin</td>
<td>Melanoma</td>
<td>25/44 [47], 5/5 [27]</td>
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<tr>
<td></td>
<td>Dermatofibroma</td>
<td>1 [117]</td>
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<tr>
<td></td>
<td>Acrochordon</td>
<td>1 [118]</td>
<td></td>
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<tr>
<td>Spleen</td>
<td>Sarcoïdosis</td>
<td>1 [119]</td>
<td></td>
</tr>
<tr>
<td>Soft tissue</td>
<td>Multiple benign and malignant</td>
<td>4: desmoid tumor [120], GIST [121], myxoma [122], nodular fasciitis [123]</td>
<td>1 [122]; 122/599 [33], 5/10 [27]</td>
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<tr>
<td>Stomach</td>
<td>Gastric adenocarcinoma</td>
<td></td>
<td>79/119 [68]</td>
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<tr>
<td></td>
<td>Thymoma</td>
<td>1 [124]</td>
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<tr>
<td></td>
<td>Papillary carcinoma</td>
<td>1, [50]; 1/1 [125], 0/1 [126]; 1/2 [127]; 61/120 [128]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follicular carcinoma</td>
<td>1 [126]; 4/4 (SUV&lt;sub&gt;max&lt;/sub&gt; 3.3–39.7) [127]</td>
<td>24/52 [128]</td>
</tr>
<tr>
<td></td>
<td>Poorly differentiated</td>
<td>1/1 [129]</td>
<td>4/8 [128]</td>
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<tr>
<td></td>
<td>Anaplastic carcinoma</td>
<td></td>
<td>4/10 [128]</td>
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<tr>
<td></td>
<td>Medullary carcinoma</td>
<td></td>
<td>4/10 [128]</td>
</tr>
<tr>
<td></td>
<td>Adenoma</td>
<td>4 [50, 130–132]</td>
<td>1 [131]; 8/43 [128]</td>
</tr>
<tr>
<td>Urinary tract and bladder</td>
<td>Carcinoma</td>
<td>1 [133]; 1/1 [134]</td>
<td>7/13 [1], 51/138 [47], 167/167 z [135], 6/6 [27]</td>
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<tr>
<td>(except kidney)</td>
<td></td>
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<tr>
<td>Vessels</td>
<td>Hemangioma</td>
<td>6: 2 × vertebrate [136, 137], 3 × liver [138] &amp; [50], subcutaneous [139]</td>
<td>1 [139]; 2/6 [33], 0/3 [27]</td>
</tr>
<tr>
<td></td>
<td>Hemangioendothelioma</td>
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<tr>
<td></td>
<td>Angiosarcoma of soft tissue</td>
<td>1 liver [140]</td>
<td>0/1 [27]</td>
</tr>
<tr>
<td></td>
<td>Atherosclerosis</td>
<td>0/150 [141]</td>
<td>3/29 [33]</td>
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<td></td>
<td></td>
<td>0/4 [141]</td>
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expression could be verified in the majority of CT-negative, PSMA-positive tumor manifestations [70]. Of the two patients with metastatic disease published by Sawicki et al., one patient had eight PSMA-PET-negative pulmonary metastases < 1 cm. This putatively reflects the well-known difficulties in detecting small lung nodules in non-breathing triggered PET that is usually compensated by the excellent sensitivity for intrapulmonary lesions of the CT component in PET/CT scanners [80]. Siva et al. performed 68Ga-PSMA-11-PET/CT in comparison to 18F-FDG-PET/CT in six patients with ccRCC, of whom five patients showed concordant sites of metastases. However, in one patient, PSMA-PET/CT could detect two additional lesions that led to a change in the therapeutic procedure. In another patient, both FDG- and PSMA-PET/CT were negative for biopsy-proven adrenal metastasis [79]. Of the published single case reports, three demonstrated superiority of PSMA-PET/CT in terms of lesion detection in comparison to FDG [69, 72, 73] and one in comparison to conventional imaging [70].

Secondary to ccRCC (80%–90%), papillary renal cell carcinoma (pRCC) (10%–15%) is the second most abundant subtype of renal cell carcinoma [147]. In contrast to ccRCC, histopathologic reports either document a low frequency and weak or even absent PSMA expression in pRCC [82–84]. Consistently, the three pRCC included in the above PET studies showed either very low or absent tracer accumulation, underlining the importance of consideration of the histopathologic renal cell carcinoma subtype for imaging with PSMA ligands [77, 79, 80].

A recent publication assessed the feasibility of PSMA-11-PET/CT for staging of adenoid cystic carcinoma (AdCC) of the salivary gland [115]. AdCC attributes for 20%–35% of salivary gland malignancies. While the rationale for PSMA imaging of tumors other than PCA usually derives from PSMA expression in the neovasculature, adenoid cystic carcinoma cells appear to express PSMA. The authors investigated nine cases of metastasized AdCC with both PSMA-PET/CT and immunohistochemistry and found PSMA-positive tumor tissue in every patient. A direct comparison with FDG-PET/CT was available in three patients and revealed inferiority in lesion detection of PSMA-PET/CT in one patient and superiority in another patient.

Histopathologic studies report a rate of PSMA expression in tumor-associated endothelium in breast cancer in 82/106 (77%) [48] and 30/44 (68%) of cases [47]. As the latter study found a substantially higher expression frequency in ccRCC of 33/34 (97%) using the same staining technique, PSMA expression rate in breast cancer can be assumed to truly range below that of ccRCC. After reporting a single case in 2015, Sathekge et al. published a prospective study of 19 women with either local or metastasized breast cancer. PSMA avidity was observed in 84% of tumor manifestations detected by previous conventional imaging and FDG-PET/CT, roughly reflecting the rate of PSMA expression as derived from ex vivo studies. In the subset of patients that additionally underwent FDG-PET/CT, only 29 of 35 (83%) FDG-avid lesions were detected with PSMA-PET/CT, whereas one lesion detected with PSMA was not FDG-avid [46].

Molecular imaging has a strong role in the management of thyroid cancer, as most thyroid cancers show avidity for iodine, whereas dedifferentiated thyroid carcinomas may lose their ability to accumulate iodine but characteristically become FDG-avid instead (flip-flop phenomenon). Conflicting reports of present or missing uptake of PSMA-targeted ligands in thyroid carcinomas in single cases have been published [50, 125, 126, 129]. Based on these findings, a recent study assessed the potential of 68Ga-PSMA-11-PET/CT imaging in six patients with iodine-negative FDG-avid metastasized thyroid cancer (four follicular, two papillary carcinoma) [127]. In three patients, FDG-PET showed superior lesion detection of whom one patient did not show any PSMA ligand uptake. Superiority of lesion detection of PSMA-PET/CT was seen in one patient. The authors concluded that PSMA-PET/CT imaging might present an alternative in patients with iodine-negative and FDG-negative differentiated thyroid carcinoma. In a recent histopathologic study, PSMA expression was attributed to about only 50% of differentiated thyroid carcinoma (63% in iodine-refractory thyroid cancer) [128]. Although the specified rate should be cautiously interpreted in light of the already exemplified discrepancies in histopathologic analyses, these results might impair the potential of PSMA-PET in thyroid carcinoma staging.

Lung cancer is still by far the leading cause of cancer death in men and women in Europe and the USA. FDG-PET/CT imaging has a widely accepted role in staging of non-small-cell lung cancer (NSCLC) due to its high sensitivity and specificity especially in determining hilar lymph node metastases. Two cases of incidental uptake in NSCLS have been described [50, 89]. A recent study retrospectively analyzed the feasibility of 68Ga-PSMA-11-PET/CT to discriminate between primary lung cancer and PCA metastasis [90]. The authors found prominent PSMA ligand uptake in all seven NSCLCs in their cohort and could demonstrate PSMA immunoreactivity of the accompanying neovasculature in every case. A larger histopathological study found PSMA expression in tumor neovasculature in 74/87 cases [91].

Not all malignancies with immunobiologically proven PSMA expression have yet been evaluated in larger cohorts of patients. These include hepatocellular carcinoma (three published incidental findings [86–88] with 90% PSMA-positive neovascularization in histopathologic studies [47], colorectal carcinoma (three incidental findings [64–66], 75–84% [1, 67, 68]), squamous cell carcinoma of the head and neck (two incidental findings [50, 62], 75% [63]), adrenocortical carcinoma (one case; 100% [28]), ovary and endometrial carcinoma (each 100% [61]).
In conclusion, PSMA-PET for staging has so far been evaluated in only a few malignant diseases other than PCA and in small patient cohorts. Although many of these studies draw positive conclusions, considering the limited numbers of patients and lack of statistical comparisons, all studies must be viewed as preliminary, and interpreted with appropriate caution. Notably, the most promising tumor entities derive from tissues with high physiological PSMA tracer uptake, i.e., clear cell renal cell carcinoma and adenoid cystic carcinoma of the salivary gland. This might complicate attempts of local staging in such diseases. Prospective studies that allow reliable quantitative assessment of the potential of staging by PSMA-PET in comparison to FDG-PET and conventional imaging should be particularly encouraged in these diseases, as the existing body of evidence available does not allow a recommendation for staging and restaging yet. Today, PSMA-PET might already be considered for ccRCC and AdCC in individual patients when conventional imaging and FDG-PET/CT have been performed and failed to delineate tumor metastasis (Fig. 1) or in exceptional cases when these imaging modalities are not feasible (intolerance of contrast medium). The results of a currently ongoing clinical study (NCT02687139) that addresses $^{18}$F–DCFPyL PET/CT in a larger cohort of patients bearing renal cell carcinoma are to be expected with highest curiosity.

The lack of consistent PSMA expression lowers the potential of PSMA imaging in tumor entities as breast cancer or thyroid carcinoma. Especially in the re-staging situation, primary tumor tissue is usually available for histopathologic investigation, PSMA expression could therefore be in principal assessed before PSMA imaging to confine PSMA imaging to patients with PSMA-positive primary tumors. Notably, histologic reports that compared PSMA expression in primary and metastatic tumor sites emphasized the resemblance of expression profiles in primary and distant tumor sites in individual patients in colorectal carcinoma [68], breast cancer [48], ovary cancer [61], and AdCC [115]. Thus, the frequently observed heterogeneity of serologic tumor markers in individual patients does not seem to apply to PSMA expression in the same extent. None of the available PSMA-PET studies explicitly considered histologically proven PSMA expression in primary tumor as an inclusion criterion for imaging, although tissue samples of primary tumor sites should have been available in most cases. Future PSMA-PET studies should consider to evaluate this approach either as a prospective inclusion criterion or to retrospectively evaluate negative PSMA-PET imaging. Future histopathologic investigators should be aware of the putative clinical relevance of the conservation of PSMA expression in different tumor sites of individual patients in respect to clinical imaging.

Expression strength and rate of PSMA is an important prerequisite but should not be the only consideration for rolling out further pilot studies for malignancies not yet analyzed in multi-patient pilot studies. Equally important is a clinical demand for a more advanced imaging technique based on an impact of lesion detection on therapeutic strategies and insufficient sensitivity and specificity of the established conventional and molecular imaging methods. For example, although PSMA has been shown to be frequently expressed in NSLCS with immunohistochemistry and PET, an advance of PSMA-PET into staging is challenged by the sufficient and established role of FDG-PET in NSCLC. One of the (yet un-examined/unpublished) tumors that seem to incorporate both features is HCC with a high frequency of PSMA expression and a so far minor role of molecular imaging (including FDG-PET) in disease staging. Consequently, an ongoing study.
(NCT03138239) investigates the potential role of $^{68}$Ga-PSMA in staging, restaging, and monitoring response in primary liver cancer.

**PSMA imaging for molecular characterization of tumors**

Lesion detection is of high importance and constitutes most clinical indications for PET imaging in oncology. However, a unique strength of molecular imaging in comparison to conventional imaging is to provide molecular information of individual lesions to predict prognosis, response to therapy, or to identify/exclude specific tumor entities in incidental findings.

Identification of patients suited for PSMA radioligand therapy of PCA is so far the only indication where molecular information derived from PSMA-PET is integrated into clinical decision-making. This would obviously apply, if PSMA radionuclide therapy is planned in diseases other than PCA (see section "Possible non-prostate field of PSMA radioligand therapy"). Despite radioligand therapy, a variety of other PSMA-targeted therapeutic approaches exist that are currently or were approached in clinical studies, including PSMA-activated prodrugs in ccRCC, glioblastoma, and hepatocellular carcinoma (ClinicalTrials.gov Identifier: NCT02607553, NCT02067156, NCT01777594) antibody-drug conjugates in glioblastoma (NCT01856933), cancer vaccines in renal cell carcinoma and other solid tumors (NCT00096629, NCT00423254), and chimeric antigen receptor T cells in bladder cancer (NCT03185468). The nature of all these highly specific PSMA-directed therapeutic approaches is a strict dependence on PSMA expression in the tumor or associated endothelium. As a means of ensuring this, PSMA-PET will likely play a role in these novel therapies, provided they will prove successful.

**Molecular characterization of neovascularization**

Angiogenesis is an essential process in tumor growth and a multitude of pharmacologic therapies primarily target angiogenesis either by affecting vascular endothelial growth factor (VEGF) ligand binding, binding of VEGF to VEGF receptor 2, or intracellular VEGF receptor 2 activation [148]. Imaging biomarkers that reflect properties of tumor-associated angiogenesis could principally serve three different functions in oncologic imaging: (1) Prognostic marker reflecting the crucial role of angiogenesis in tumor development, (2) prospective estimation of therapy response to anti-angiogenic drugs, (3) therapy monitoring of anti-angiogenic drugs or other therapeutic modalities. The potential of PSMA as an imaging biomarker for these applications is connected to the exact functional role of PSMA in tumor-associated endothelium. PSMA is not a prerequisite for tumor-associated neovascularization as it is not consistently found with it. Its frequent expression in especially those tumor entities that critically depend on angiogenesis (ccRCC, ovarian cancer, hepatocellular carcinoma), however, associates a relevant role of PSMA and substantiates its potential to reflect tumor properties of actual clinical relevance. A series of recent publications aimed to track down PSMA function in angiogenesis [149–151]. The authors substantiated that PSMA exerts its exopeptidase activity on small peptides derived from cleavage of the extracellular matrix component Laminin by the endopeptidase matrix metalloproteinase-2. PSMA-mediated cleavage of a C-terminal glutamate converts these peptide fragments into agonists that activate integrins (e.g., $\alpha_2\beta_1$, $\alpha_3\beta_1$) and focal adhesion kinase signaling to promote endothelial cell activation and angiogenesis. These results appear highly reasonable in light of the significant contribution of other membrane-bound exopeptidases in tumor-associated angiogenesis [151]. However, these mechanistical insights into PSMA function do not yet allow to deduce its functional relevance relating to tumor aggressiveness and susceptibility to anti-angiogenic therapy regimens.

**PSMA as a predictor for prognosis**

Most of the publications that histopathologically examined PSMA expression in different tumors also correlated its expression to markers of prognostic relevance which revealed high heterogeneity between different PSMA-expressing tumor types. In squamous cell carcinoma of the head and neck, Haffner et al. found a strong and significant difference in overall survival between patients with low vs. high endothelial PSMA expression (77 vs. 18 months; $p = 0.0001$). After adjusting for grade and stage, high PSMA expression remained an independent marker for poor prognosis (hazard ratio (HR) = 2.19, 95% confidence interval (CI) 1.2–3.9, $p = 0.007$) [63]. In osteosarcoma, PSMA expression not only significantly correlated with tumor size and presence of lung metastasis but also with worse cumulative overall survival (5-year survival PSMA negative 63.2%, PSMA positive 36.6%, $p < 0.05$) [32]. In breast cancer, PSMA expression showed significant correlation with indicators of more aggressive tumor grades (nuclear grade, Ki-67 index, estrogen receptor-negative, progesterone receptor-negative), tumor size and a mild significant negative correlation with overall survival (OS) (10-year survival PSMA weak/negative 96%, PSMA strong 79.7%, $p = 0.05$) [48]. In colorectal cancer, Haffner et al. found a mild, but significant, positive correlation with PSMA expression and high-grade tumors, an effect on survival was not observed [68]. Additionally, Abdel-Haidi et al. found a positive correlation with presence of metastasis and vascular invasion, but not with other clinicopathological markers (tumor size, grade, local extent, lymph node deposits etc.) [67]. In adenocarcinoma of the pancreas, a significant
positive correlation of PSMA expression with histological grade and pTNM stage and consequently a negative relationship with prognosis was observed (OS with weak PSMA 13 months vs. strong PSMA 8 months, \( p < 0.01 \)) [102]. In ccRCC, a multivariable Cox analysis revealed an independent association between PSMA-positivity and poor overall survival (HR 2.02, 95% CI 1.08–3.79, \( p = 0.028 \)), as well as a significant positive relationship with high T-, M-, R-, and International Society of Urologic Pathologists (ISUP) grades [84]. In lung cancer, Wang et al. found a low correlation of PSMA expression and clinical stage, but no significant correlation with tumor size or lymph nodal status [91]. In thyroid cancer, PSMA positivity was significantly correlated with tumor size and vascular invasion in follicular thyroid carcinoma, however, no association with other features as extrathyroidal extension, metastasis, and American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) stage was noted [128]. Neither in gastric cancer [68], nor in adrenocortical carcinoma [28] was a significant positive relationship with high T-, M-, R-, and International Society of Urologic Pathologists (ISUP) grades [91]. In thyroid cancer, PSMA positivity was significantly correlated with tumor size and vascular invasion in follicular thyroid carcinoma, however, no association with other features as extrathyroidal extension, metastasis, and American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) stage was noted [128]. Neither in gastric cancer [68], nor in adrenocortical carcinoma [28] was a significant association with tumor grade or disease stage observed. In conclusion, PSMA expression appears to reflect prognostically relevant tumor features for several, but not all, PSMA-expressing tumor entities. Whether the correlation with prognosis is reflected by PSMA-PET is speculative today, since up to now no clinical publication has reported on prognostic factors derived from PET imaging. Especially in squamous cell cancers of the head and neck, ccRCC, osteosarcoma, and breast cancer, existing histopathological data appears promising. However, the future of utilizing PSA-PET as a prognostic marker in non-prostatic cancer will ultimately depend on a clinical demand on prognostic information and that these cannot be sufficiently gathered by other prognostic markers or histopathological examination of PSMA expression alone. However, regardless of the future role of PSMA-PET imaging in determining prognosis, significant correlations document a relevant change of tumor biology associated with PSMA expression pointing to an important functional role of endothelial PSMA expression.

**PSMA as a predictor of antiangiogenetic therapy response**

Although different anti-angiogenic drugs have been shown to prolong progression-free as well as overall survival for various malignant diseases, the overall effects were rather modest. A recent review concluded that “a crucial need remains for substantial research of predictive biomarkers” [148] and the above-mentioned associations of PSMA and tumor endothelium make PSMA-PET a promising method for this approach. A major drawback is that apparently murine model organisms do not show PSMA expression in xenograft tumor-associated endothelium, impeding preclinical approaches. To date, no PET studies have been published that valuate the potential of PSMA as an imaging biomarker for tumor-associated angiogenesis in the context of planned or performed anti-angiogenetic therapy. Considering the expense in time and cost of prospective, longitudinal studies that could answer these questions, a straight and feasible first step would be to correlate PSMA expression with established neovascularization biomarkers. One candidate for histopathologic approaches is determination of the microvascular density (MVD), which just has gained increasing attention due to its significant correlation with bevacizumab therapy benefit in respect to progression-free and overall survival in ovarian cancer [152, 153]. Of the many studies cited above, however, only a minor fraction performed or published such a statistical comparison, although nearly all studies performed co-staining with the endothelial markers CD34 and CD31 that allow estimation of the MVD. MVD and PSMA were (to our knowledge) only tested for correlation in squamous cell carcinomas of the head and neck, which revealed a strong positive correlation with MVD (\( p = 0.002, V = 0.34 \)) [63]. In Bychkov et al., MVD and PSMA were shown not to be spatially correlated in individual samples, indicating no association between overall PSMA and MVD, although no patient-based correlation was performed [128].

The currently most established imaging biomarkers in the context of anti-angiogenic therapy derive from dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) studies. In particular, the transfer constant \( K^{\text{trans}} \), which reflects the vascular permeability and endothelial surface area, is attributed a role in predicting and monitoring therapy response [154]. DCE-MRI and PSMA-PET could principally be simultaneously performed in PET/MRI scanners, allowing for direct correlation of these markers. In experimental PET, various potential molecular targets have been investigated and are subject of current investigations, amongst them specific integrins with involvement in angiogenesis [155, 156]. Recalling that function of PSMA expression in angiogenesis is attributed to activation of the integrins \( \alpha_2\beta_1 \) and \( \alpha_3\beta_1 \) [151] emphasizes its potential as an imaging biomarker for angiogenesis.

Thus, besides the difficulties of a preclinical evaluation, there are multiple approaches to substantiate the potential of PSMA-PET as a biomarker for angiogenesis and especially correlation of PSMA expression with histopathologicic biomarkers as MVD should be emphasized in the future, considering the relative straightforwardness of this technique. However, prospective longitudinal studies are needed to ultimately determine if endothelial PSMA is really embedded in molecular cascades relevant to anti-angiogenic therapy. A currently performed pilot study (NCT02978586) uses \(^{68}\)Ga-PSMA PET/MRI for the assessment of short-term (2–6 weeks) response monitoring in PSMA-positive PCA, lung cancer, and breast cancer undergoing systemic therapy.
PSMA imaging to identify or rule out pathologic entities

Another potential utilization of PSMA-PET is to differentiate between specific pathologic entities, e.g., between benign and malignant tumors in incidentalomas. As the non-specificity of PSMA in respect to PCA imaging is the basis of this review article, PSMA-PET seems to be a poor instrument to differentiate PCA metastasis from other malignancies. For example, a recent study aimed to utilize PSMA-PET to differentiate PCA lung metastases from lung cancer and failed so because of the consistent PSMA expression in NSCLC [90]. Vice versa, frequent reports of benign lung lesions including infectious and inflammatory changes [79, 90, 92, 93] challenge the role for PSMA-PET to identify or rule out malignancy in incidential lung nodules, especially in consideration of the well-established role of FDG-PET in this domain.

A recent study demonstrated that adrenocortical carcinoma (ACC) displayed a nine- and ten-fold higher PSMA expression in ACCs when compared with normal adrenal tissue and adrenocortical adenoma (AA) samples, as determined by qPCR. Immunostainings found moderate or high PSMA expression in the endothelium of 13/15 ACCs and weak, but present expression in 2/15. In contrast, 0/16 normal adrenal glands and 2/16 AAs showed weak PSMA staining [28]. The recent incidental finding of an adrenal adenoma with PET/CT [29] does not contradict these results considering the high prevalence of incidentally discovered adrenal masses and AAs amongst those. Considering the low rate of PSMA expression in benign lesions and the consistent expression in ACC, PSMA-PET could play a role in ruling out ACC, and thus potentially spare biopsy taking. Notably, however, the investigated tumors AA and ACC only represent a subset of benign and malignant tumors that represent incidentalomas of the adrenal gland. Other primary adrenal gland tumors such as pheochromocytomas have not been systematically investigated for PSMA positivity. Additionally, a high proportion of adrenal gland tumors present with distant metastases, which should display similar patterns of PSMA expression in correspondence to their primary tumor. Current practice guidelines for adrenal gland incidentalomas recommend FDG-PET/CT as an option when non-contrast CT could not identify benign imaging features [157] and it is characterized by high sensitivity, but only intermediate specificity to detect malignant tumors [158]. Again, prospective clinical PET studies would allow a definitive assessment of the role of PSMA-PET in characterizing incidentalomas.

PSMA for molecular characterization of cerebral tumors

Brain metastases were found in 1.6% of PCA patients in an autopsy study [159] and detection of putative PCA brain metastases using PSMA-PET/CT has been reported [160]. In addition, employment of PSMA-PET for other tumor entities that more often metastasize to the brain (as ccRCC) or primary brain tumors requires a closer look on the properties of current PSMA-PET tracers in intracranial imaging. High-grade gliomas are interesting candidates for PSMA-PET imaging considering the unclarified role of anti-angiogenic therapies in these tumors. In addition, glioblastoma (GBM) is the target of clinical studies that use PSMA-activated produgs (NCT02067156) and PSMA antibody drug conjugates (NCT01856933). Three different studies utilized PSMA-PET to characterize the molecular profile of cerebral tumors in terms of PSMA expression, and lesional PSMA-PET positivity was observed in every case [53–55]. The utilized $^{68}$Ga- and $^{18}$F-PSMA PET tracers are hydrophilic substances with very little intracranial accumulation in the healthy brain despite expression of PSMA in astrocytes [11, 59, 161] reflecting their inability to sufficiently penetrate the blood–brain barrier either by diffusion or active transport. This associates two important implications on intracranial PSMA-PET: (1) PSMA-PET tracers likely depend on an impairment of the blood–brain barrier to reach and bind PSMA expressed by tumor cells, challenging their sensitivity in detecting intracranial PSMA-positive lesions, (2) PSMA-PET tracers are likely to passively accumulate in areas of a dysfunctional blood–brain barrier (equivalent to hydrophilic CT and MRI contrast media), challenging their specificity in intracranial imaging. The first implication is rather of theoretical nature, as brain metastases usually feature a dysfunction of the blood–brain barrier that should allow tracer diffusion to tumor cells. However, especially treatment with VEGF-antibodies (e.g., bevacizumab) can at least partially restore blood–brain barrier integrity [162]. Whether impairment of the blood–brain barrier is a prerequisite for targeting endothelial PSMA expression critically depends on the polar localization of PSMA in endothelial cells (apical or basolateral) which, to our knowledge, has not been investigated to date. The second implication, that focal blood–brain barrier damage is putatively sufficient to produce contrast, is of critical importance for PSMA imaging of intracranial structures and should be considered and discussed in scientific and clinical approaches targeting primary or secondary brain tumors with PSMA-PET. Two studies have reported focal PSMA-PET/CT tracer accumulation following stroke [57, 58]. Although post-stroke inflammation inducing PSMA expression is reasonably discussed, focal dysfunction of the blood–brain barrier appears to be a likely cause for these findings. The awareness for this issue is reflected by the efforts of Salas Fragomeni et al. and Schwenck et al. in correlating PSMA-PET uptake with site-specific biopsies, which demonstrated consistent overlapping PSMA expression. However, PSMA is mostly expressed in endothelial cells, which are the cellular determinants of blood–brain barrier dysintegrity. Thus, colocalization of PSMA tracer
accumulation and (histochemical) PSMA-positive endothelium would not only result from specific tracer binding but be also highly likely in the case of passive tracer accumulation due to focal blood–brain barrier dysintegrity. Site-directed biopsies can thus not be interpreted as proof of the specificity of the observed tracer accumulation. Notably, the exhibited images in Salas Fragomeni et al. and Schwenck et al. show a striking colocalization of Gd-DTPA enhancement in MRI and PET tracer accumulation. In conclusion, signal specificity of current $^{68}$Ga- and $^{18}$F–PSMA-PET tracers in intracranial imaging is currently not sufficiently studied and should therefore be interpreted with a high degree of caution. Other strategies to segregate specific from unspecific uptake are needed to reliably characterize PSMA expression of intracranial tumors. One approach to do so is currently employed in a clinical study (ClinicalTrials.gov Identifier: NCT02410577), where an $^{89}$Zr-labeled PSMA antibody (J591) is used to image PSMA expression in patients with glioblastoma multiforme. The long radioactive half-life of $^{89}$Zr allows imaging over several days after tracer injection, which should not be as susceptible to passive tracer accumulation effects.

Utilization of physiologic uptake features

Physiologic PSMA expression is found in prostatic epithelium [1], a subset of proximal kidney tubules [1], the luminal site of parts of the small intestine [1], the salivary glands [116] and a subset of astrocytes [59]. This pattern derived from immunostainings is only partially reflected by PET, as radiotracer distribution is not a strict function of PSMA expression, but also reflects tracer-specific barriers, glandular tracer excretion, and tracer metabolism. Thus, in addition to the mentioned PSMA expression foci, PSMA-PET activity is observed in the liver, spleen, and urine, whereas nearly no tracer activity is detected in brains with intact blood–brain barriers. Whereas numerous studies have addressed the diagnostic challenges deriving from physiologic PSMA-PET tracer distribution in PSMA imaging, we want to challenge its potential in this chapter.

In PSMA-PET using current $^{68}$Ga- and $^{18}$F–tracers, kidneys are usually the organ with the strongest tracer accumulation, followed by the salivary glands [11]. Consistent with the equivalent distribution of therapeutic PSMA radioligands as $^{177}$Lu-PSMA-617, the kidneys and salivary glands are exposed to the highest doses and are considered the critical organs in PSMA radionuclide therapy [163]. For both organs, either laboratory or clinical monitoring are therefore highly recommended with facultative functional scintigraphies ($^{99m}$Tc-MAG3 and $^{99m}$Tc-pertechnetate), e.g., by the consensus paper of the German Society of Nuclear Medicine [164]. PSMA-PET is recommended before therapy and after every two cycles, and salivary glands and kidneys are usually included in the field of view. It thus would appear very convenient if sufficient information on renal and salivary function could be directly assessed from PSMA uptake features of these glands, either by contralateral or longitudinal comparison or even by absolute SUV quantification. Additionally, the recent introduction of $^{90m}$Tc-PSMA tracers might provide alternatives to the currently utilized conventional tracers for clinical questions unrelated to PSMA radionuclide therapy. Different tracers exist for renal scintigraphy that are supposed to reflect distinct, yet connected properties: tubular excretion (e.g., $^{99m}$Tc-MAG3), glomerular filtration (e.g., $^{99m}$Tc-DTPA) and vital cortical kidney tissue (e.g., $^{99m}$Tc-DMSA). From all we know, the current PSMA tracers might most closely mimic $^{99m}$Tc-DMSA, since it similarly specifically binds to cells of the proximal tubule [1]. However, PSMA tracers are also to a varying degree excreted into urine, so that intrarenal urine activity will add to the specifically bound tracer. Considering that PSMA is expressed at the luminal (=urinal) side of the tubule cells [1], a further contribution to the signal of urinal flow and PSMA excretion appears likely, as higher urine tracer concentration would facilitate specific binding and higher urine flow would promote tracer unbinding. To date, however, no studies have been published that investigated whether and which functional properties are reflected by renal PSMA accumulation. As in kidneys, PSMA expression in the salivary glands should reflect specific tracer binding, however, a role of salivary excretion cannot be excluded. In contrast, salivary scintigraphy with $^{99m}$Tc-pertechnetate solely reflects excretion of the gland. Currently, no published studies exist that link PSMA-PET tracer uptake to functional properties of the salivary gland in the context of PSMA-radioligand therapy.

Possible non-prostate field of PSMA radioligand therapy

In recent years, PSMA-targeted radioligand therapies, mainly $^{177}$Lu-PSMA-617, have shown respectable response rates with a favorable toxicity profile in patients with metastasized castration-resistant cancer at a very late stage of disease [165–169]. To date, no report of PSMA radioligand therapy in non-PCA disease has been published. PSMA is located on the cancer cell membrane in PCA whereas in most other tumors it is solely or majorly located in the tumor-associated endothelium. This leads to an increased distance between radiation emitter and tumor cell that would likely decrease the probability of an emitted electron to affect a tumor cell (beta emitter $^{177}$Lu with a mean electron range in tissue of 670 μm [170]). Surely, this effect would be far more pronounced for alpha emitters such as $^{225}$Ac with a maximum range in tissue well below 100 μm [171, 172]. Whether this disadvantage could be counterbalanced by radiation damage of the neovascularature can only be speculated. High and consistent
tracer uptake is a prerequisite for successful radioligand therapy. Figure 2 shows a patient with late-stage iodine refractory thyroid cancer evaluated. It must be emphasized that the respectable uptake in PSMA-PET observed in some non-PCA tumors is only a snapshot in time that occurs usually in the first 2 h after tracer injection. In contrast to radionuclide imaging, however, radionuclide therapy critically depends on long-lasting tumor association of the radionuclide. In PCA, a fraction of PSMA radioligands is internalized into the cell, contributing to a high radiation dose. To date, no data exist that allow deducing the temporal slope of therapeutic PSMA-ligand binding to the endothelium. Systematic future studies should evaluate uptake and retention of beta-emitting PSMA radioligands in dosimetry studies to potentially open the field of PSMA radioligand therapy to other tumor entities.

Conclusions and future perspectives

The prostate-specific membrane antigen is not specific for the prostate, as several benign and malignant entities have been reported by imaging and histologic studies to show a relevant expression of PSMA, especially in tumor-associated endothelial cells. As was reviewed here, this opens a window of opportunity to novel fields for PSMA-PET with respect to staging, molecular characterization, and maybe even radioligand therapy of non-prostatic tumors.

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Compliance with ethical standards

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Conflict of interest The authors declare that they have no financial or non-financial competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

References


