Imaging for Prostate Cancer Recurrence

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Abstract

Context: Correct identification of metastatic sites in recurrent prostate cancer (PCa) is of crucial importance because it leads to further treatment decisions.

Objective: To provide an overview on current imaging procedures and their performance in recurrent PCa.

Evidence acquisition: Medline search via PubMed was performed with the keywords imaging, recurrent, and prostate cancer as well as more detailed searches including the keywords bone scan, bone scintigraphy, computed tomography, magnetic resonance imaging, positron emission tomography, PET, choline, FDG, prostate-specific membrane antigen, and PSMA, with emphasis on recent literature from 2010 to the present. Non-English published literature was excluded. Abstracts and full-text articles were reviewed and assessed for relevant content.

Evidence synthesis: In diagnostic imaging and particularly with newer technologies like positron emission tomography (PET), a profound lack of prospectively designed studies in recurrent PCa has to be noted. In most studies histologic validation has only been performed in a subset of patient cohorts. Heterogeneity of included patient cohorts, lack of standardized assessment, as well as diverging end points, hamper systematic comparison of different image modalities. Thus evidence for currently used imaging in recurrent PCa is only presented descriptively.

Conclusions: Computed tomography and magnetic resonance imaging (MRI) as well as bone scintigraphy still represent the standard imaging for recurrent PCa; however, particularly for detection of local recurrence, multiparametric MRI is a valuable imaging modality. PET using choline and particularly tracers against prostate-specific membrane antigen might improve visualization of metastatic lesions. These findings need to be validated in prospective trials.

Patient summary: Imaging of recurrent prostate cancer (PCa) is important to guide further treatment. Computed tomography, magnetic resonance imaging, and bone scintigraphy represent the current standard. Positron emission tomography, especially with cancer–specific tracers, might improve imaging of recurrent PCa in the future.

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1. Introduction

Between 27% and 53% of all patients undergoing radical prostatectomy (RP) or radiotherapy (RT) for primary treatment of prostate cancer (PCa) develop biochemical recurrence (BCR) [1]. However, among patients with BCR, heterogeneous progression risks exist [2,3]. Specifically, a better survival was recorded in patients with nodal recurrence compared with patients with bone or visceral metastasis after primary treatment [4]. The early addition of docetaxel to androgen-deprivation therapy alone recently emerged as an effective therapy in patients harboring a high burden of metastatic hormone-sensitive cancer [5,6]. Similarly, also in patients harboring hormone-insensitive castration-resistant cancer, a precise staging is necessary for the right timing and the selection of treatment regimen.

Tremendous advances in magnetic resonance imaging (MRI) techniques and the availability of functional/metabolic imaging allow earlier visualizing of PCa recurrence [7]. Further refinements of these techniques and the combined use of morphologic imaging with functional positron emission tomography (PET) imaging might enable the urologist to individualize treatment in patients with recurrent PCa.

Based on the increasing availability of novel sophisticated but expensive imaging modalities, it is mandatory for urologists to know the diagnostic accuracy of these techniques. We outlined the current different modalities for the imaging of recurrent PCa and their potential use as well as their limitations.

2. Evidence acquisition

In the preparation of this nonsystematic review, we performed a Medline search via PubMed with the keywords imaging, recurrent, and prostate cancer, as well as more detailed searches including the keywords bone scan, bone scintigraphy, computed tomography, magnetic resonance imaging, positron emission tomography, PET, choline, FDG, prostate-specific membrane antigen, and PSMA, with an emphasis on recent literature from 2010 to the present. Non-English published literature was excluded. Abstracts and full-text articles were reviewed and assessed for relevant content. The references of retrieved full-text articles were included for the consideration of relevant articles. In general, and particularly with newer technology like PET, a profound lack of prospectively designed studies in recurrent PCa has to be noted. The heterogeneity of included patient cohorts as well as end points also hampers systematic comparison of the different image modalities.

In most studies, histologic validation (if any) was performed only in a subset of patient cohorts. In most of those histologically validated subsets of patients, little was reported on the pathologic work-up (eg, application of immunohistochemistry staining). This is especially important because series with a less diligent histologic work-up (eg, without immunostaining) automatically detect a biased high sensitivity of a method, potentially misleading urologists in their daily clinical practice. In PCa patients, however, up to 37% of tumor deposits are <2 mm and are often only detected after sophisticated histologic examination [8,9]. Consequently, the standardized definition and performance of pathologic examination as well as close collaboration of imaging specialists, urologists, and pathologists is mandatory within the interdisciplinary validation process. For all these reasons, interpretation and comparison of different imaging modalities must be performed with caution.

3. Evidence synthesis

3.1. Multiparametric magnetic resonance imaging

3.1.1. Detection of local recurrence after radical prostatectomy

Computed tomography (CT) is no longer recommended for depicting locoregional relapse of PCa after RP or RT owing to its poor contrast resolution. On the contrary, MRI, thanks to its inherent superior contrast and spatial resolution, is of great value to evaluate prostatic fossa after RP. Multiparametric MRI (mpMRI) is able to discriminate between locoregional relapse and a small amount of residual glandular healthy tissue or scarred, fibrotic, and granulation tissue (Fig. 1), and it may even be useful to assess the aggressiveness of nodule recurrence by means of apparent diffusion coefficient (ADC) values [10]. The presence on T2-weighted (T2w) images of a lobulated, semicircumferential, nodular- or plaque-like soft tissue thickening in the prostatectomy bed that appears slightly hyperintense compared with pelvic muscles should be considered suggestive of local recurrence [11,12]. When conventional T2w is not able to discriminate between local recurrence and postoperative changes, dynamic contrast-enhanced (DCE) sequences are of paramount importance for the differential diagnosis [13]. A recurrent tumor tends to enhance quickly and avidly in the arterial phase, which is followed by a plateau or washout on the signal intensity (SI) curve during the venous phase. Postoperative changes tend to show either no enhancement or mild enhancement in the venous phase [11].

Thus mpMRI can be currently considered the most reliable imaging biomarker to detect local PCa recurrence in patients with biochemical failure after RP that is crucial for the planning of salvage RT [14], particularly for those prostate-specific antigen (PSA) values at which PET/CT is not recommended (0.2–1 ng/ml) [15,16] (Table 1).

3.1.2. Detection of local recurrence after radiotherapy

In patients with local recurrence after RT, salvage therapies generally involve treatment of the entire prostate because the exact location of the recurrent tumor within the prostate is unknown [17]. At present, mpMRI is widely considered the state-of-the-art imaging modality. After RT, because of shrinkage and induced glandular atrophy and fibrosis, the peripheral, central, and transition zones appear less distinct from each other due to diffusely decreased SI on T2w imaging. T2w alone is of limited diagnostic accuracy because the recurrent tumor as well as normal surrounding parenchyma both appear hypointense. For instance, mpMRI
Fig. 1 – (A–C) Set of images of a 63-yr-old man with recurrent prostate cancer (PCa) after radical prostatectomy (RP; prostate-specific antigen [PSA]: 0.53 ng/ml). (A) Axial T2-weighted fast spin-echo image shows a solid nodular tissue of about 5 mm in size on the left posterior perianastomotic location that is slightly hyperintense compared with pelvic muscles (arrow). (B) Axial apparent diffusion coefficient (ADC) map reconstructed from images obtained at b-values of 0, 500, 1000, and 3000 s/mm$^2$ shows restricted diffusion (dark area) corresponding to the abnormal hyperintense tissue seen on T2-weighted images (arrow). (C) Axial gradient-echo T1-weighted color map image shows a remarkable enhancement of the pathologic tissue (arrow). All these findings are consistent with locoregional relapse. (D–F) Set of images of a 69-yr-old man with recurrent PCa after RP (PSA: 0.6 ng/ml). (D) Axial T2-weighted fast spin-echo image shows a solid nodular tissue of about 8 mm in size on the posterior perianastomotic location that is slightly hyperintense compared with pelvic muscles (arrows). (E) Axial ADC map reconstructed from images obtained at b-values of 0, 500, 1000, and 3000 s/mm$^2$ shows no restricted diffusion (bright area) corresponding to the abnormal hyperintense tissue seen on T2-weighted images (arrows). (F) Axial gradient-echo T1-weighted color map image shows inhomogeneous enhancement of the abnormal tissue detected on T2-weighted images (arrows). All these findings are consistent with residual glandular healthy tissue.

ADC = apparent diffusion coefficient; PCa = prostate cancer; PSA = prostate-specific antigen; RP = radical prostatectomy.

utilizing DCE can easily discriminate between postradiation fibrosis that shows homogeneous, slow, and low enhancement and recurrent tumor that can be recognized as a hypervascular early-enhancing homogenous nodule [18,19]. DCE, however, should be performed at least 3 mo after RT because an increase in perfusion and blood volume due to inflammatory reactions of the tissue to RT is usually present immediately after treatment [11]. Concerning magnetic resonance spectroscopy (MRS), voxels with spectra containing no significant metabolite peaks, specifically spectra having a peak area-to-noise ratio <5:1 for choline, polyamines, creatine, and citrate, represent the so-called metabolic atrophy that is highly indicative of a successful and effective treatment [11]. Persistent or recurrent disease is defined as a choline-to-creatinine ratio >1.5:1, whereas others use the standard choline plus creatine/citrate ratio for discrimination. For instance, Panebianco et al. proved that MRS follow-up, using the choline plus creatine/citrate ratio, shows a greater potential compared with PSA in monitoring patients after RT because MRS is able to detect PCa recurrence or residual disease before BCR occurs [20]. Concerning diffusion-weighted imaging (DWI), the significant difference in ADC values between tumors and benign tissues before RT disappears after treatment. One possible explanation is that, after RT, benign tissues might show histologic changes such as acinar distortion, atrophy, stromal fibrosis with granulation tissue formation, and inflammatory swelling of prostate cells that might result in a decrease in ADC values, whereas the tumor shows an increase of ADC values. Donati et al. analyzed a patient population of 53 men with BCR after RT [21]. They showed that for detecting locally recurrent PCa, combined T2w and DWI provided significantly better diagnostic accuracy (area under the receiver operating characteristic curve [AUC]: 0.75–0.86) than T2w alone (AUC: 0.46–0.67) and that the addition of DCE to T2w and DWI did not improve diagnostic accuracy. Thus currently mpMRI with DWI and DCE represents the most useful sequences for detecting recurrent tumor after RT (Table 1).
<table>
<thead>
<tr>
<th>Study</th>
<th>Modality</th>
<th>No. of patients</th>
<th>Main study findings</th>
<th>Authors’ conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sciarra et al. [13]</td>
<td>MRI (MRS, DCE)</td>
<td>50</td>
<td>For identification of local recurrent PCa after RP (biopsy confirmed); MRS and DCE showed an AUC at ROC analysis of 0.942 and 0.931. Combination of DWI and MRS increased diagnostic accuracy (AUC: 0.964)</td>
<td>MRI with combined DWI and MRS accurately identifies local recurrent PCa after RP</td>
</tr>
<tr>
<td>Crillo et al. [12]</td>
<td>MRI (T2w, DCE)</td>
<td>72</td>
<td>DWI showed a sensitivity, specificity, and accuracy of 84.1%, 89.3%, and 86.1% compared with 61.4%, 82.1%, and 69.4% for sole T2w for identification of local recurrent PCa after RP</td>
<td>DWI improves the diagnostic performance compared with sole T2w</td>
</tr>
<tr>
<td>Panebianco et al. [10]</td>
<td>MRI (T2w, DWI, DCE)</td>
<td>242</td>
<td>For identification of local recurrent PCa after RP (biopsy confirmed), T2w and DCE showed a sensitivity, specificity, and accuracy of 100%, 97%, and 91% compared with 98%, 96%, and 89% for T2w and DWI. In a cohort confirmed by PSA follow-up after RT, these values were 98%, 94%, and 93% for T2w and DCE compared with 97%, 95%, and 93% for T2w and DWI</td>
<td>DCE is the most reliable technique in detecting local PCa recurrence after RP, although DWI can be proposed as a reliable alternative</td>
</tr>
<tr>
<td>Donati et al. [21]</td>
<td>MRI (T2w, DWI, DCE)</td>
<td>53</td>
<td>For identification of local recurrent PCa after RT (biopsy confirmed), T2w and DWI performed significantly better than sole T2w (p &lt; 0.014). DCE sequences did not contribute significant incremental value to T2w and DWI</td>
<td>Addition of DWI or DCE to T2w significantly increases accuracy for detection of recurrent PCa after RT</td>
</tr>
<tr>
<td>Panebianco et al. [15]</td>
<td>MRI (MRS)</td>
<td>50</td>
<td>MRS during follow-up after RT correctly identified 43 patients who responded to RT, 5 patients who recurred, and 2 patients who had persistent disease preceding the diagnosis of biochemical relapse</td>
<td>MRS has greater potential than PSA level in monitoring patients after RT because it anticipates PSA nadir and biochemical relapse</td>
</tr>
<tr>
<td>Cimian et al. [42]</td>
<td>11C-Cho PET/CT</td>
<td>100</td>
<td>46/100 patients (PSA: 0.12–14.3 ng/ml) without lesions on PET/CT (89% of patients with PSA &lt; 4 ng/ml and 87% of patients with Gleason score &lt;8)</td>
<td>No significant impact in patients with BCR of PCa if PSA &lt; 4 ng/ml but may be helpful to rule out systemic disease in selected cases</td>
</tr>
<tr>
<td>Krause et al. [43]</td>
<td>11C-Cho PET/CT</td>
<td>63</td>
<td>Dr of lesions on PET/CT was 36% for PSA &lt; 1 ng/ml, 43% for PSA 1 to &lt; 2 ng/ml, 62% for PSA 2 to &lt; 3 ng/ml, and 73% for PSA ≥ 3 ng/ml</td>
<td>DR of PET/CT shows a positive relationship with PSA levels in patients with BCR of PCa</td>
</tr>
<tr>
<td>Giovacchini et al. [44]</td>
<td>11C-Cho PET/CT</td>
<td>109</td>
<td>In patients with BCR of PCa and uneventful conventional imaging, DR of PET/CT was 11%. PSA was the only predictor of positive PET/CT</td>
<td>PET/CT may be useful for restaging but cannot be used to guide therapy</td>
</tr>
<tr>
<td>Mitchell et al. [49]</td>
<td>11C-Cho PET/CT</td>
<td>176</td>
<td>In 32% of patients with BCR of PCa, PET/CT identified lesions not detected by conventional imaging. Trigger PSA (HR: 1.37; p = 0.04) and initial clinical stage (HR: 5.19; p = 0.0035) were significant predictors of positive PET/CT</td>
<td>The optimal PSA value for DR is approximately 2.0 ng/ml. PET/CT substantially enhances DR compared with conventional imaging at lower PSA</td>
</tr>
<tr>
<td>Marzola et al. [47]</td>
<td>18F-Chol PET/CT</td>
<td>233</td>
<td>DR of lesions on PET/CT increases significantly with higher PSA. PET-positive patients presented with accelerated PSA kinetics (mean PSA DT = 6 mo vs 15.4 mo; mean PSA velocity = 9.3 ng/ml per year vs 0.9 ng/ml per year)</td>
<td>In about 20% of patients, detection of lesions by PET/CT enabled locoregional radiation therapy</td>
</tr>
<tr>
<td>Afshar-Oromieh et al. [55]</td>
<td>68Ga-PSMA</td>
<td>319</td>
<td>DR of PET/CT was positively associated with PSA level and ADT, but not with Gleason score and PSA DT. Histologic confirmation in 42 patients showed a sensitivity, specificity, NPV, and PPV of 76.6%, 100%, 91.4%, and 100% on a lesion-based analysis</td>
<td>PET/CT detects recurrent PCa in a high number of patients. Radiotracer is highly specific for PCa</td>
</tr>
<tr>
<td>Eber et al. [56]</td>
<td>68Ga-PSMA</td>
<td>248</td>
<td>DR of lesions on PET/CT was 57.9% for PSA 0.2 to &lt; 0.5 ng/ml, 72.7% for PSA 0.5 to &lt; 1 ng/ml, 93.0% for PSA 1 to &lt; 2 ng/ml, 96.8% for PSA ≥ 2 ng/ml. Compared with conventional imaging, PET showed exclusively pathologic findings in 32.7% and additional involved regions in 24.6% of patients</td>
<td>PET/CT shows substantially higher DR than reported for other imaging modalities especially at low PSA (&lt;0.5 ng/ml)</td>
</tr>
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</table>

ADT = androgen deprivation therapy; AUC = area under the curve; BCR = biochemical recurrence; Cho = choline; CT = computed tomography; DR = detection rate; DWI = diffusion-weighted imaging; F = fluorodeoxyglucose; Ga = gallium; HR = hazard ratio; MRS = magnetic resonance spectroscopy; NPV = negative predictive value; PCa = prostate cancer; PET = positron emission tomography; PPV = positive predictive value; PSA = prostate-specific antigen; PSA DT = prostate-specific antigen doubling time; PSMA = prostate-specific membrane antigen; ROC = receiver operating characteristic; RP = radical prostatectomy; T2w = T2-weighted.
3.1.3. Detection of lymph node and bone metastases

Whole-body MRI including whole-body DWI outperforms bone scan (BS) in detecting recurrent bone metastasis and has the same diagnostic performance of total-body CT for the evaluation of lymph nodes (LNs) [22]. The use of lymphotropic superparamagnetic iron oxide nanoparticle contrast agents can improve the sensitivity and specificity of MRI for the detection of LN metastases. The diagnostic accuracy is increased if DWI is performed [23,24].

3.2. Bone scintigraphy and sodium $^{18}$F-fluoride positron emission tomography for detection of bone metastases

Bone imaging with 99m technetium (Tc)-phosphonates or sodium $^{18}$F-fluoride plays an important role in the management of PCa patients according to current guidelines [1,25]. Both agents depict increased osteogenic activity induced by osteoblastic bone metastases. Adding single-photon emission computed tomography (SPECT) and computed tomography (SPECT/CT) to plain BS has shown to reduce the number of equivocal lesions [26]. For therapy response, BS offers the ability of a fast whole-body overview that in addition can be used for quantification (eg, Bone Scan Index [BSI] [27]). Scher et al. showed that the BSI, however, is more likely than other variables to identify bone lesions as stable disease, even when those variables indicate a beneficial response [28]. With the use of automated BSI scoring, this tool has the potential to provide objective reader-independent information that could make patient cohorts more comparable [29].

Problems in BS arise from the so-called flare phenomenon induced by treatment of bone metastases due to increased activity of osteoblasts that can lead to a false-positive diagnosis of disease progression. Thus if BS is the sole indicator of progression, the Prostate Cancer Working Group 2 (PCWG2) defines progression when at least two or more new lesions are seen compared with a prior scan [30]. For situations in which the scan findings are suggestive of a flare reaction or an apparent new lesion may represent trauma, it may prove useful to confirm these results with other imaging modalities such as MRI or multislice CT. Newer recommendations adopting the PCWG2 criteria suggest confirmation of progressive disease when two more additional lesions are present at a confirmatory scan [31]. Consistent criteria for progression of disease in bone using PET are still under investigation.

Another bone imaging agent represents sodium $^{18}$F-fluoride. This PET tracer exhibits several advantages over single-photon planar imaging and SPECT including higher resolution and the capability of reduced scanning time leading to improved detection of bone metastases. In the study by Schirrmeister et al, sodium $^{18}$F-fluoride PET was more sensitive (100%) than planar 99mTc bone scanning (54%) and SPECT (92%) in 12 patients with bone metastases [32]. Similar results were obtained by Even-Sapir et al. in 2006, who studied 44 men with high-risk PCa using sodium $^{18}$F-fluoride PET/CT and 99mTc-diphosphonate with a multiple field-of-view SPECT [26]. In the patient-based analysis, the sensitivity and specificity of PET/CT versus SPECT were 100% versus 92% and 100% versus 82%, respectively. Notably, in both studies, the performance of mere 99mTc-diphosphonate BS was poor (Fig. 2).

The National Oncologic PET Registry evaluated sodium $^{18}$F-fluoride of 20 238 patients. A report on a subset including only patients with PCa encompassing 3531 scans in 3396 patients shows that sodium $^{18}$F-fluoride PET/CT substantially affected intended management [33]. PET/CT had a high overall impact, primarily related to replacing intended use of other advanced imaging in about half of the cases. More significantly, patient management after sodium $^{18}$F-fluoride was changed in 44–52% of patients. After adjustment for those cases for which both the pre-PET plan as well as other advanced imaging may have led to the same changes, the impact of sodium $^{18}$F-fluoride on management was still 12–16%.

A comparison between 99mTc-diphosphonate BS, sodium $^{18}$F-fluoride, and $^{18}$F-choline PET/CT resulted in a sensitivity and specificity of 51% and 82% versus 93% and 54% versus 85% and 91%, respectively [34].

3.3. Positron emission tomography imaging with fluorodeoxyglucose, choline, and other metabolic tracers

Fluorodeoxyglucose (FDG) is the most widely used PET tracer, and therefore it has been tentatively used to study PCa since the 1990s. However, due to poor sensitivity, FDG has been demonstrated to be of limited value [35]. In the largest study, FDG PET was reported to be useful in detecting disease in only a small number of patients with PCa recurrence [36]. FDG PET/CT may be most useful in detecting aggressive disease, the evaluation of extent and treatment response in metastatic disease, and in the prognostication of a castrate-resistant clinical state [37].

Despite being considered a new radiopharmaceutical, choline has been proposed as a tracer for PCa for almost 2 decades [38]. Choline can be labeled with either $^{11}$C or $^{18}$F-fluoride, and it is the most widely used PET tracer. At present a large number of original studies are available with conflicting results (Table 1). Data were frequently not considered satisfactorily for a mixture of similar but different radiopharmaceuticals ($^{11}$C-choline, $^{18}$F-fluorocholine, and $^{18}$F-fluoromethylcholine), studies with different patient populations, lack of prospective and multicenter studies, and difficulties in identifying a reference standard for PET findings, among others [39–41]. Some papers reported a limited diagnostic performance [42–44]. In recent years several attempts have been made to perform meta-analyses on choline studies in PCa [40,41,45] and even comparisons with other tracers [39]. Currently, choline PET/CT is not recommended in patients with BCR and a PSA level <1 ng/ml, but it might be of value at higher PSA levels or PSA kinetics [1].

3.3.1. Overall performance in biochemical recurrent prostate cancer

Evangelista et al. [45] reported a pooled sensitivity of 85.6% (95% confidence interval [CI], 83–88) and pooled specificity of 92.6% (95% CI, 90–95); they aggregated data from $^{11}$C-choline and $^{18}$F-choline and finally included 19 studies.
heterogeneity was noted. Most of the original studies reported data for detection rate, thus not comparing PET results with a true reference standard but with correlative imaging. Fanti et al. [40] found the detection rate of \(^{11}\)C-choline PET/CT for any site of PCa relapse to be 62% (95% CI, 53–71), lower than pooled sensitivity. These figures are in line with our routine clinical experience.

3.3.2. Detection of local recurrence

By aggregating data on local relapse, Evangelista et al. reported a pooled sensitivity of 75% (95% CI, 66–82) and a pooled specificity of 82% (95% CI, 69–91) [45]. Fanti et al. found a pooled sensitivity of 61% (95% CI, 40–80); pooled specificity was 97% (95% CI, 87–99) [40]. These results indicate a high variability for both sensitivity and specificity, and overall data seem insufficient to draw final conclusions. However, performance of choline PET/CT for local recurrence is likely to be inferior to MRI, especially when multiparametric sequences are applied.

3.3.3. Detection of lymph node metastases

For LN detection, Evangelista et al. reported a pooled sensitivity of 100% (95% CI, 90–100) and a pooled specificity of 81.8% (95% CI, 48–98) [45]. These numbers, however, are derived from four studies including only cases with histologic examination. It implies a relevant bias of patient inclusion because only cases with a very high likelihood of LN relapse were enrolled and submitted to salvage LN dissection. Conversely, Fanti et al. reported an overall detection rate of 36% (95% CI, 22–50) from seven original studies, with very high heterogeneity between studies [40] (Fig. 3).

3.3.4. Detection of bone metastases

In the meta-analysis by Fanti et al. overall detection rate was 25% (95% CI, 16–34), with again very high heterogeneity between studies [40]. Shen et al. performed a meta-analysis on choline PET in PCa bone metastases and reported a pooled sensitivity of 91% (95% CI, 83–96) and a pooled specificity of 99% (95% CI, 93–100) by aggregating data from \(^{11}\)C-choline and \(^{18}\)F-choline [46]. They also reported superior values of sensitivity for MRI (pooled sensitivity 97% with 95% CI, 91–99), in line with comparative studies reporting better performance of mpMRI imaging compared with choline PET/CT for identifying bone lesions.

3.3.5. Current role of choline positron emission tomography

Although the evaluations of accuracy at different sites of recurrence report a limited detection rate for choline PET, these data have to be regarded positively. Choline PET/CT, despite suboptimal sensitivity, is currently still the only widely distributed imaging method allowing to evaluate all of the sites as a “one-stop shop” examination.

It has been demonstrated that choline PET detection rate is related to PSA values. After the first report of Krause et al. [43], several authors confirmed this finding, and moreover they demonstrated that PSA kinetics are probably the strongest predictor for a positive PET scan [47].

Fig. 2 – Set of images of a 69-yr-old patient with recurrent prostate cancer after radical prostatectomy and local radiation therapy and a prostate-specific antigen value of 2.4 ng/ml at the time of imaging. (A) Bone scintigraphy shows no suspicious findings for bone metastases. The focal intense uptake at the transition between the cartilaginous and osseous part of the fifth and sixth rib (arrow) represents a typical pattern of previous bone rib fractures. (B) Maximum intensity projection (MIP) of a choline scan shows no bone lesions. The intense uptake in the region of the left upper chest (arrows) is related to retained tracer activity in the subclavian/axillary vein as was proven by computed tomography (CT). (C) MIP of a prostate-specific membrane antigen (PSMA) scan and (D) fused PSMA positron emission tomography/CT show a focal intense tracer uptake projecting on the os ileum (arrow); (E) a corresponding CT does not show abnormalities. (F) On follow-up CT, the initiation of antihormonal treatment development of sclerotic changes was noted, likely showing treatment response of a small bone metastasis.

CT = computed tomography; MIP = maximum intensity projection; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen.
meta-analysis was aimed at specifically addressing such a relationship [48]. They reported that PSA doubling time \( \leq 6 \) mo and PSA velocity \( > 1 \) or \( > 2 \) ng/ml per year proved to be relevant factors in predicting the positive result of a choline PET/CT examination.

Implications of such a relationship are largely questionable: a lower sensitivity of choline PET at PSA values \( < 1 \) ng/ml, although true, does not imply lack of usefulness in this subset of patients [44,49]. The diagnostic accuracy of a test should not be regarded as the sole criteria to establish clinical relevance. Clinical role and the capability to affect patient management are probably more important. Patients who may be appropriate for early salvage local therapy (salvage external-beam radiation therapy of lymphadenectomy) could benefit from choline PET/CT even at low PSA values, whereas in patients with high PSA values who are unsuitable for salvage local therapy, the role of imaging studies is very debatable.

The suboptimal sensitivity of choline PET could be overcome only by developing radiopharmaceuticals more specific for PCa. A number of tracers have been developed for this purpose. One of the most interesting, \(^{18}\)F-FACBC (also known as \(^{18}\)F-fluciclovine), is a synthetic amino acid tested since 2007 to study PCa. Recent investigation reported a better sensitivity and specificity compared with choline PET [50], thus suggesting a potential role for this tracer in identifying PCa recurrence.

3.4. Positron emission tomography imaging with prostate-specific antigen membrane-targeted tracers

Another promising target for PET imaging of recurrent PCa represents the prostate-specific membrane antigen (PSMA) that shows increased expression on most PCa cells compared with normal prostate tissue. However, PSMA is not exclusive for PCa; expression has also been described in other benign and malignant conditions [51]. Several small-molecule tracers directed against PSMA were recently developed providing favorable characteristics for imaging [52]. In contrast to the previously described agents that image metabolism, tracers directed against PSMA detect its molecular expression independently of metabolic or inflammatory changes. After binding they are internalized and show fast blood clearance and hence low background activity. Currently, the most widely used new-generation PSMA PET imaging agent represents the \(^{68}\)Ga-labeled PSMA
inhibitor Glu-NH-CO-NH-Lys(Ahx)-HBED-CC ($^{68}$Ga-PSMA HBED-CC) [53,54].

3.4.1. Overall performance in biochemical recurrent prostate cancer
In 2015, two large studies were published on PSMA PET/CT using $^{68}$Ga-PSMA HBED-CC in recurrent PCa (Table 1) [55,56]. In the study by Afshar-Oromieh et al, almost 83% of 319 patients (226 after RP, 93 after irradiation therapy) with a median PSA value of 4.6 ng/ml showed at least one lesion typical for PCa (Fig. 4). Of note, even at low PSA values, suspicious lesions were detected: in 50% of patients with PSA values <0.5 ng/ml and in 58% of patients with PSA values from 0.5 to 1 ng/ml. In their study, initial Gleason score as well as the administration of hormone-deprivation therapy did not significantly influence detection rates [55].

In the study by Eiber et al., 248 consecutive patients with BCR after RP and a median PSA value of 1.99 ng/ml received PET/CT using $^{68}$Ga-PSMA HBED-CC [56]. Suspicious lesions were detected in 89.5% of these patients. As for choline-based PET, a correlation of the absolute PSA value and the detection rate was observed. Detection rates increased from 57.9% over 72.7%, 93.0–96.8% for PSA values of 0.2 to <0.5, 0.5 to <1, 1 to <2, and >2 ng/ml. Compared with standard diagnostic CT, PSMA PET significantly enhanced the detection rates in this study (Fig. 5). In 32.7% of patients, only PSMA PET revealed suspicious findings, and in 24.6% it showed additional involved anatomic sites (Fig. 6). Diagnostic CT, in contrast, exclusively detected suspicious lesions only in 1.2% of patients and additional lesions in 6.9%. In this study, detection rates increased with higher PSA velocity (81.8%, 82.4%, 92.1%, and 100% in <1, 1–2, 2–5, and >5 ng/ml per year, respectively) but showed no significant association with PSA doubling time (82.7%, 96.2%, and 90.7% in >6, 4–6, and <4 mo, respectively). In contrast to the study by Afshar-Oromieh et al, detection efficacy was significantly increased in PCa patients with higher initial Gleason score. Because PSMA-based PET detects PCa lesions at low PSA values <0.5 ng/ml, it might significantly affect further clinical management such as the planning of targeted volume during salvage irradiation as another recent study by Leeuwen et al. demonstrated [57].

3.4.2. Potential future role of prostate-specific membrane antigen-targeted positron emission tomography
The main limitation of these studies, however, represents the fact that only in a subset of patients (42 patients in the study by Afshar-Oromieh et al. and 12 patients in the study by Eiber et al.) could histologic confirmation be obtained. In all those patients, though, all PSMA PET–positive lesions
were also histologically confirmed as PCA metastases. The successful establishment of PSMA-radioguided surgery underlines the high specificity of PSMA PET. During this procedure PSMA ligands labeled with gamma-emitting $^{111}$Indium are utilized for intraoperative tracking and detection of metastatic soft tissue lesion by PCA [58]. Thus it can be expected that further studies including greater patient cohorts with recurrent PCa and histologic correlation will confirm the high specificity of PSMA PET because first reports in primary PCa have already proved the high specificity of preoperative PSMA PET [59,60]. In a first comparative study, $^{68}$Ga-PSMA HBED-CC was reported to be superior to $^{18}$F-fluoromethylcholine PET/CT. In this analysis including 37 patients with recurrent PCa, $^{68}$Ga-PSMA HBED-CC showed all lesions visible with $^{18}$F-fluoromethylcholine, but it also detected suspicious lesions in six patients in whom $^{18}$F-fluoromethylcholine PET was negative [61].

In the future, modification of PSMA tracers could further advance imaging of PCa with respect to dispersion of the technique, ease of production, as well as image resolution. In an initial case series, $^{18}$F-DCCPyL, a second-generation fluorinated PSMA ligand, proved to be advantageous compared with $^{68}$Ga-PSMA HBED-CC based PET imaging in patients with recurrent PCa [62].

4. Conclusions

Imaging in recurrent PCa is of crucial importance because it guides further therapy. Standard imaging in recurrent PCa includes CT, MRI, and bone scintigraphy. Although CT and MRI do not differ significantly for LN staging, MRI with multiparametric sequences is particularly useful for detecting local recurrent disease [11].

By the addition of DWI and DCE sequences to T2w MRI, local recurrent tumor can be discriminated from residual healthy or scar tissue [10]. Thus mpMRI currently can be considered the most reliable imaging tool to detect local recurrent PCa [15,16]. For the detection of bone lesions, whole-body MRI outperforms CT and BS [22].

BS depicts bony lesions depending on size and metabolism and offers a fast and inexpensive whole-body imaging that can be easily quantified by the use of the BSI [27]. SPECT/CT can further improve classification of equivocal lesions [26]. Sodium $^{18}$F-fluoride PET shows a higher resolution as well as increased sensitivity and
specificity compared with BS [34]. However, it is not widely available and can only be used for visualization of bone lesions.

Newer PET tracers investigated in PCa include choline-based tracers that can enable imaging of bone as well as soft tissue lesions like LNs or visceral metastases. Enhanced detection rates and improved staging of metastatic disease for choline-based tracers have been demonstrated [40,41,45]. However, choline-based PET still lacks the ability to identify smaller or less metabolic lesions, especially at low PSA values. Initial reports on PET imaging with tracers against PSMA suggest improved visualization of recurrent PCa lesions even at low PSA values [55,56]. However, these findings need to be validated in prospective trials relying on standardized pathologic work with the most recent techniques. Thus joint efforts have to be undertaken to design and execute those prospective trials and thus obtain the evidence required for implementation into clinical guidelines.

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Study concept and design: Maurer, Eiber, Fant, Budäus, Panebianco.

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Analysis and interpretation of data: Maurer, Eiber, Fant, Budäus, Panebianco.

Drafting of the manuscript: Maurer, Eiber, Fant, Budäus, Panebianco.

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