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A paradigm shift from anatomic to functional and molecular imaging in the detection of recurrent prostate cancer

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Abstract

Approximately a third of men with localized prostate cancer who are treated with external beam radiation therapy (EBRT) or radical prostatectomy (RP) develop biochemical failure (BF). Presumably, BF will progress to distant metastasis and prostate cancer-specific mortality in some patients over subsequent years. Accurate detection of recurrent disease is important because it allows for appropriate treatment selection (e.g., local vs systemic therapy) and early delivery of therapy (e.g., salvage EBRT), which affect patient outcome. In this article, we discuss the paradigm shift in imaging technology in the detection of recurrent prostate cancer. First, we discuss the commonly used morphological and anatomical imaging modalities and their role in the post-RP and post-EBRT settings of BF. Second, we discuss the accuracy of functional and molecular imaging techniques, many of which are under investigation. Further studies are needed to establish the role of imaging techniques for detection of cancer recurrence and clinical decision-making.

Keywords

CT; MRI; PET; prostate cancer; radiology; recurrence

Background

Prostate cancer is the most common noncutaneous malignancy and second leading cause of cancer death among men in the USA [1]. The incidence of prostate cancer rose after the introduction of prostate-specific antigen (PSA) screening. Consequently, approximately 80% of men diagnosed in the USA present with localized (i.e., T1–T2) disease [2]. For men with

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localized prostate cancer, treatment with external beam radiation therapy (EBRT) or radical prostatectomy (RP) is largely successful at controlling disease [3]. However, approximately a third of men develop biochemical failure (BF) [4,5], typically defined by a rise in serum level of PSA of 0.2 ng/ml after RP or nadir + 2 ng/ml after EBRT [6]. Presumably, BF will progress to distant metastasis (DM) and prostate cancer-specific mortality over subsequent years. Accurate detection of recurrent disease is important because it allows for appropriate treatment selection (e.g., local vs systemic therapy) and early delivery of the therapy (e.g., salvage EBRT), which favor patient outcome [7].

The goal of performing imaging in patients with BF is to rule out the presence of metastatic disease, which could obviate the need for local radiation therapy (RT) and argue for the use of systemic therapy. As of 2013, most models for detecting recurrent prostate cancer depend on pretreatment characteristics, including PSA, Gleason score and T-stage [6,8]. Notably, radiologic imaging is not included in these algorithms because of certain limitations. First, current imaging modalities often cannot consistently or reliably detect the source of PSA for early, low-PSA-level BF [9,10]. Potential sources of detectable PSA in the context of BF may include local recurrence (LR), lymph node metastases (LNMs), DMs, a combination of sites or benign prostatic tissue (e.g., post-EBRT PSA bounce; benign prostatic hyperplasia). Second, recurrent disease (especially LR) may appear differently on radiographic modalities, depending on the primary treatment used. Finally, there is variability in morphological criteria (e.g., size and shape) of a suspected region of interest [9], while numerical PSA cut-offs are absolute and may also be integrated with other factors in multivariable prediction algorithms.

In this article, the paradigm shift of imaging technology in the detection of recurrent prostate cancer is discussed. First, we evaluate the commonly used morphological and anatomical imaging modalities and their role in the post-RP and post-EBRT settings. Second, we discuss the accuracy of functional and molecular techniques under investigation and focus on the limitations of imaging modalities (e.g., restriction to particular patient populations) and how these implications may influence clinical decision-making. Finally, we discuss the variations and marketing approval of imaging modalities around the world, including the USA (the origin of this article) and Europe.

Search strategy

For analysis of functional and molecular imaging techniques, we defined inclusion criteria for the literature search using the Population, Intervention, Control, Outcome, Study Design (PICOS) approach (Box 1) [11]. We conducted a systematic search using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) literature selection process (Figure 1). We searched the published English medical literature from 1970 until 2013 in MEDLINE and PubMed using the terms ‘prostate cancer’, ‘recurrence’ and ‘imaging’. After identifying full-text articles, we excluded review articles, articles focusing on the initial diagnosis of prostate cancer, articles not reporting sensitivities or specificities in detection of recurrent disease, and articles focusing primarily on pharmacokinetics or safety of methods. In total, 46 articles were included in this review, falling under the following categories: multiparametric MRI, defined as the combination of traditional T₂-

weighted imaging with one or more functional techniques (e.g., spectroscopy, dynamic contrast enhancement, diffusion weighing, and lymphotropic nanoparticles) [12–22]; single-photon emission computed tomography (SPECT) [23–30]; and PET [31–57]. Almost all patients in the identified articles were treated with primary RP or EBRT; thus, for both sections of this review (i.e., ‘Role of anatomic imaging in the detection of recurrent prostate cancer’ and ‘Role of functional and molecular imaging in the detection of recurrent prostate cancer’), we focus on imaging of BF after these two treatment modalities.

Role of anatomic imaging in the detection of recurrent prostate cancer

Available anatomic imaging modalities

Currently, there is no uniformly accepted imaging modality that can distinguish local from systemic recurrence [9,10,58,59]. Traditional imaging modalities to evaluate recurrent disease include the following: radionuclide skeletal scintigraphy (‘bone scan’); transrectal ultrasound (TRUS)-guided biopsy; computed tomography (CT) scan; and MRI. The guidelines for the use of these imaging modalities in the setting of BF after RP and EBRT are summarized in Table 1. In general, these techniques may detect macroscopic disease, but they have poor sensitivity for very low volume disease, or when PSA is <10 ng/ml.

^{99m}Tc-methyl diphosphonate skeletal scintigraphy (‘bone scan’)

A ‘bone scan’ with ^{99m}Tc-labeled methyl diphosphonate (^{99m}Tc-MDP) is probably the most common study requested in the setting of a rising PSA level after RP [9]. The main advantages of a bone scan are its high sensitivity, ability to scan the entire skeleton and low cost. However, a bone scan also has low specificity because the tracer accumulates in benign bone disease (e.g., degenerative joints), which are often present in elderly men.

After RP, a bone scan is most useful in patients with a rapidly rising PSA (e.g., >0.5 ng/ml/month) [64,68–69]; only 26% of patients have a positive scan with a PSA doubling time (PSA-DT) <6 months [68]. Additionally, the probability of a positive bone scan is <5% unless PSA is >40 ng/ml [70]; 4% if PSA is <10 ng/ml [61,71] and 0% if the PSA is <7 ng/ml [69]. Notably, these PSA values are taken in the absence of adjuvant androgen deprivation therapy and are higher than the level when salvage therapy is considered [6].

In the post-RP setting, Beresford *et al.* recommend a bone scan in the following settings [9]: PSA-DT <6 m; PSA velocity >0.5 ng/ml/month; absolute baseline PSA >10 ng/ml; symptoms of bone disease. Additionally, a nomogram to predict the likelihood of a positive bone scan may be used [61]. Factors considered include postoperative PSA, Gleason score, surgical margins, PSA velocity and PSA-DT. In the post-EBRT setting, the National Comprehensive Cancer Network (NCCN) recommends a bone scan in certain men who are candidates for local salvage therapy [60].

TRus-guided biopsy

In the post-RP setting of BF, a TRUS-guided biopsy is most likely to be positive in the vesicourethral anastomosis, followed by the anterior bladder and neck [9]. After RP, a biopsy of the prostatic fossa has a sensitivity of approximately 75% and specificity of

approximately 66%, which is higher than a digital rectal examination alone [72,73]. However, if the PSA is <1 ng/ml, sensitivity drops to 14–45% [73,74]. After EBRT, when the prostate appears diffusely hypoechoic, the detection of LR on TRUS-guided biopsy is difficult (sensitivity: 49%; specificity: 57%), with detection rates close to digital rectal examination (sensitivity: 73%; specificity: 66%) in predicting a positive postirradiation biopsy [75,76]. Multiple biopsies are necessary to increase the sensitivity >90% [77]. In either setting, TRUS-guided biopsy has a low sensitivity and does not rule out the possibility of DM. TRUS-guided biopsies are commonly performed in the workup of BF because there is no absolute PSA cut-off value to accurately predict on an individual basis if a patient has LR and/or systemic disease [78]. However, after RP, TRUS-guided biopsy is generally not recommended [9,60], and after EBRT, it is only recommended for certain men who are candidates for salvage focal therapy [9,60]. Notably, color/power-Doppler TRUS may be able to improve the distinction between recurrent cancer and post-RP fibrosis (sensitivity: 40–93%; specificity: 85–100 %) [62,63]. Combining color/power-Doppler with MRI may reduce the number of biopsies [63].

CT of abdomen & pelvis

In the post-RP situation, men with BF have a positive CT <15% of the time [64]. Notably, surgical scar tissue may be confused with LR [9]. A CT is may be performed in the setting of BF after RP as it may help define salvage EBRT target volumes [64] and evaluate for nodal disease [9,60]. However, in most cases (e.g., when PSA is <5–10 ng/ml) CT is not routinely recommended after EBRT or RP.

T₁/T₂-weighted MRI

In an untreated prostate, T₂-weighted MRI provides best depiction of prostate zonal anatomy and capsule. After either RP or EBRT, wholebody MRI is superior to bone scintigraphy in the detection of DM. Although MRI may help define target volumes for salvage EBRT, at least one multiparametric MRI technique is typically needed with anatomic MRI to detect LR [58].

In the post-RP setting of BR, MRI is recommended in patients with a high risk of LR, including those with positive surgical margins, extracapsular extension or seminal vesicle involvement [9]. However, the study is not essential as salvage EBRT is routine. In the post-EBRT setting of BF, contrast between benign irradiated tissues and recurrence cancer is decreased, making detection of LR more difficult [58].

An endorectal MRI is commonly used to increase the signal-to-noise ratio and optimize signal reception. In the post-RP setting, an MRI with an endorectal coil can improve sensitivity and specificity of identifying LR to >95% [67]. Additionally, endorectal coil MRI may better define target volumes for EBRT and detect seminal vesicle remnants. In the post-EBRT setting, there is limited data for the use of an endorectal coil, and it has been postulated to increase rectal toxicity [58].

Traditionally, MRI for prostate cancer has been performed with a 1.5 T scanner and endorectal coil, which appears to be more accurate than the use of 0.3 or 0.5 T scanners [79]. With the introduction of higher field strength (e.g., 3 T) and therefore higher spatial

resolution, the endorectal surface coil can be used less frequently, which may make MRI more accessible [14]. Nonetheless, the field strength of MRI is only one factor that may influence detection rates of prostate cancer; other factors include the use of dedicated coil designs (i.e., endorectal coils), contrast and speed [80]. Thus, although a 3 T MRI shows a high accuracy for the staging of clinically localized prostate cancer [81], it is currently unknown whether improved spatial resolution and signal-to-noise ratio of 3 T scanners improves diagnostic performance in the setting of prostate recurrence over 1.5 T scanners [82]. In summary, of the imaging modalities currently available, whole-body MRI is the most sensitive for detecting DM; endorectal coil MRI may be the best for detecting LR after RP, although its accuracy after EBRT has not yet been fully investigated. MRI and CT may both be used to plan salvage EBRT target volumes, although CT is otherwise not recommended. A bone scan has PSA-dependent recommendations after RP. CT and bone scan have low diagnostic value in patients considered for salvage therapy, who typically have low PSA levels. A TRUS-guided biopsy is typically not recommended in either setting because of poor sensitivity.

Guidelines regarding imaging modalities

The NCCN has no clear recommendations for imaging in BF after RP [60]. The NCCN recommends a biopsy and bone scan for certain men who are candidates for local therapy in BF after EBRT (i.e., those with T₁-T₂, N_{X/0} disease and life expectancy >10 years). The European Association of Urology (EAU) similarly states that routine imaging of stable patients is not recommended [83]. Specifically, the EAU recommends TRUS and biopsy only if it will affect the treatment plan; however, they stress that, in most cases, TRUS and biopsy are not necessary before second-line therapy (evidence strength: grade B). The EAU states that although metastases may be detected by pelvic CT/MRI or bone scan, these examinations may be omitted in asymptomatic patients if the serum PSA level is <20 ng/ml (evidence strength: grade C). Finally, they recommend against routine imaging studies in asymptomatic patients; in symptomatic patients, they state that a bone scan may be considered irrespective of serum PSA (evidence strength: grade B) [83].

The American Urologic Association (AUA) and American Society for Radiation Oncology (ASTRO) released joint guidelines for imaging in the setting of BF after RP [84]. They state that in a patient with a PSA recurrence, a restaging evaluation may be considered (evidence strength: grade C) [84]. The organizations caution clinicians that the yield of some modalities (e.g., bone scan) is extremely low in patients with PSA values <10 ng/ml.

Role of functional & molecular imaging in the detection of recurrent prostate cancer

A number of other imaging modalities are under investigation. Studies from the PICOS/PRISMA protocol (Box 1 & Figure 1) included in this review are summarized in Table 2. In the following section, we discuss the reported usefulness of functional and molecular imaging modalities and their restrictions to particular patient populations. Per our search criteria, we summarize the reported sensitivities and specificities of various modalities after EBRT and RP. Additionally, each modality has distinct benefits for detecting LR, LNMs and

DMs; thus, we explain how each modality is theorized to be useful in detecting recurrence at particular sites.

Notably, there are currently no guidelines from the NCCN [60], EAU [83] or the AUA and ASTRO [84] regarding the use of functional or anatomic imaging. The AUA and ASTRO state that making concrete recommendations is difficult because in many of the reviewed studies:

- No recurrence could be identified in a subset of patients with BF by either a reference standard or the modality under investigation;
- There is use of different reference standards;
- There is failure to administer a reference standard to all patients;
- There is a lack of independence of the reference standard from the evaluated modality;
- There is a lack of blinding test interpreters;
- There are relatively small sample sizes (<50 men for most study arms).

Multiparametric MRI

The development of prostate cancer is associated with changes in cellular metabolism, diffusion and blood flow. Multiparametric MRI aids in the detection of these changes. The functional techniques that are combined with traditional T₂-weighted MRI include spectroscopy, diffusion weighted (DW) imaging, dynamic contrast-enhanced (DCE) imaging and lymphotropic nanoparticle MRI. The studies included in this section were published from 2004 to 2012; thus, they typically use 1.5 or 3 T magnet. Given the limited number of studies using MRI overall, it is currently unknown whether improved spatial resolution and signal-to-noise ratio of 3 T MRI improves diagnostic performance over a 1.5 T MRI [82]. Additionally, three of the multiparametric MRI modalities (i.e., magnetic resonance spectroscopy [MRS], DCE and DW imaging) in this section have potential to more accurately detect LR; their potential in detecting LNM or DM is largely unreported. Lymphotropic nanoparticle (LTNP) MRI, by definition, is meant to detect only LNM.

Magnetic resonance spectroscopy

MRS measures relative concentrations of metabolites (e.g., choline, citrate and creatinine). MRS may differentiate between prostate cancer and normal tissue or necrotic tissue; thus, the primary goal of MRS has been to detect LR. After primary therapy, MRS has a reported sensitivity of 56–89% compared with the 68% of MRI alone in detecting LR [12–15]. Additionally, MRS has good correlation with biopsy data [12,13]. However, MRS is limited by poor spatial resolution high sensitivity to field inhomogeneities induced by surgical clips. Moreover, the best diagnostic criteria in MRS reads are still unclear since normal citrate is in theory undetectable after RP, thus making the classic choline-to-citrate ratio inaccurate [10]. The future of MRS may be restricted to high-risk patients; for example, Zakian *et al.* found that MRS was more sensitive in men with Gleason scores ≥ 6 [15], while Hom *et al.* found

that tumors with a Gleason score of 6 that were not detected with MRS had relatively small diameters [85].

DCE-MRI

DCE-MRI enables the evaluation of vascular parameters (e.g., flow and permeability) by measuring early gadolinium washout in prostate cancer [86]. After injection of gadolinium, the signal intensity of prostate tissue is measured as a function of time. The underlying tissue permeability and microvascular flow can be calculated by comparison with a nearby artery. DCE-MRI purportedly can therefore detect locally recurrent tumors in which an angiogenic pathway has been turned on, with tumor-associated angiogenesis and increased microvessel density [87].

Compared with T₂-weighted MRI alone, DCE-MRI after EBRT has a sensitivity of 95 versus 88% and a specificity of 85 versus 80% in the detection of LR [16]. Compared with T₂-weighted MRI alone, DCE-MRI after RP has a sensitivity of 84–94% versus 48–61% and a specificity of 75–100% versus 52–82% in the detection of LR [14,17–19]. Additionally, DCE-MRI shows favorable contrast between poorly vascularized post-RT fibrosis and hypervascular cancer recurrence, and it has a better correlation with biopsy results than those from T₂-weighted MRI [16,86]. Unfortunately, vascularity and contrast enhancement can be reduced in patients who have received androgen deprivation, which may limit the application of the technique [9]; and the necessity of gadolinium contrast may preclude use in patients with renal insufficiency.

DW-MRI

DW-MRI may be a more simple technique that does not require contrast and instead quantifies the water motion in an indirect manner by measuring proton diffusion properties within water. Intraductal and extracellular water molecules move freely; by contrast, extracellular space is decreased in prostate cancer and the apparent diffusion coefficient of water molecules is low. Thus, DW-MRI indirectly measures the degree of cellular crowding. DW-MRI has therefore been under investigation to more clearly define LR. After EBRT, DW-MRI compared with T₂-weighted MRI alone, has a sensitivity of 62 versus 25% and a specificity of 97 versus 92% in detecting LR [20]. After RP, a Swiss cohort study showed that DW-MRI detected LR in five men, later proven by biopsy [21].

LTNP-MRI

In LTNP-MRI, LN-avid supraparamagnetic iron oxide nanoparticles are distributed among the nodal architecture, where they are internalized by macrophages. In 26 men who were candidates for salvage RT post-RP, LTNP MRI was well tolerated, and six patients who were previously believed to be node negative tested lymph node positive [22]. Additionally, in a trial of 80 men who had primarily intermediate- and high-risk disease with localized prostate cancer, 334 LNs were resected or underwent biopsy at the time of surgery; LTNP-MRI had a positive predictive value of 95% and a negative predictive value of 98%, significantly better than MRI [88]. LTNP-MRI is limited in that: it requires two imaging sessions within 24 h (i.e., one to administer the contrast agent and one to acquire images); the contrast agent is

still investigational; and there are no studies comparing the accuracy of LTNP-MRI with other imaging modalities

Hybrid imaging using radionuclide emission tomography

Radionuclides (radioactive isotopes) linked to functional molecules are used in emission tomography. Radionuclide hybrid imaging modalities combine anatomical imaging data (typically from CT) with radionuclide SPECT or PET/CT. In either PET/CT or SPECT, a variety of radionuclides with different half-lives may be used [71,89–90]. In SPECT, attenuation reduces the number of photons received by the γ -camera from the organ of interest, causing relatively poor image quality. In PET/CT, tomographic whole-body images are acquired with a typical resolution of 5 mm. MRI/PET is being explored, but it has not yet been reported in publications meeting the criteria applied to search the literature. Nonetheless, the potential of MRI/PET for imaging patients with BF has been reported and appears promising [56].

Reported sensitivities and specificities of radionuclide imaging techniques are listed in Table 2. Radionuclide characteristics are summarized in Table 3. Metabolic functions and prostate cancer-specific proteins detected with radionuclides are illustrated in Figure 2. Unlike techniques using multiparametric MRI, molecular imaging using radionuclides may detect LR, LNM and DM, depending on the molecule and isotope.

Radioimmunoscintigraphy

Radioimmunoscintigraphy (RIS) uses radiolabeled monoclonal antibodies specific for prostate cancer epitopes. Tracers currently used bind to prostate-specific membrane antigen (PSMA), which is expressed more so in malignant than benign prostate cells. RIS depends on the degree of biomarker expression (i.e., PSMA) rather than the size of lesion or the degree of PSA expression.

ProstaScint™ (^{111}In -capromab pendetide) is a murine IgG monoclonal antibody that binds to the intracellular epitope of PSMA on prostatic epithelial cells, but not to secretory glycoproteins (e.g., PSA and prostatic acid phosphatase). After RP, ProstaScint has a sensitivity of 75–86% and a specificity of 47–86% in detecting LR [23–28]. Some studies have also noted its ability to detect LR, DM and LN disease [26–27,91].

However, others have noted that ProstaScint cannot detect bone metastases [92,93], probably because it only recognizes the intracytoplasmic site of PSMA and may not localize to intact viable cells, but only necrotic cells. Additionally, men with a positive scan after RT have no difference in progression-free survival compared with those with a negative scan [23,25,94]. Moreover, the positive predictive value of ProstaScint is only 27–50%, as inflammation and vascular perturbations from surgery may be read as a positive scan [8,27,91,94]. Based on the currently published literature, ProstaScint scans should not be used in recommending salvage RT after RP [8,23,25,94].

The use of ProstaScint may also be limited due to the high background expression of PSMA in normal tissue, the possibility that internal binding may occur mainly in necrotic or apoptotic cells (where the antibody would bind to the intracellular portion of PSMA), and

the suboptimal targeting efficiency of the radioisotope with SPECT rather than PET. J591, labeled with ^{111}In or ^{177}Lu , is a monoclonal antibody targeting the extracellular domain of PSMA, and it has provided improved imaging of bony metastases and prostatic fossa when conjugated to radioisotopes [29]. The value of J591 in detecting recurrent cancer has not been extensively studied [30].

Small molecules

^{18}F -FDG— ^{18}F -fluorodeoxyglucose (^{18}F -FDG) is the most commonly used radiotracer for PET/CT in oncology. ^{18}F -FDG is indicated for poorly differentiated, fast-growing cancers [89]. In prostate cancer, ^{18}F -FDG has relatively low uptake (secondary to a low glycolysis rate) and high bladder uptake due to renal excretion, which mask the prostatic parenchyma and limit its utility. The masking cannot be resolved by continuous rinsing of the bladder via a catheter or the use of furosemide [95]. Additionally, ^{18}F -FDG cannot reliably differentiate among prostate cancer recurrence, benign prostatic hyperplasia or scar tissue, and it is dependent on PSA values. Thus, ^{18}F -FDG is not used to detect LR, but has potential to detect LNM or DM [32,95]. After RP or EBRT, ^{18}F -FDG PET sensitivity in detection of LNM or DM ranges from 50 to 80% and its specificity from 72 to 100% [31–34].

^{11}C -choline & ^{18}F -choline—Choline is converted by choline kinase to phosphorylcholine and incorporated into cell membrane phosphatidylcholine during cellular proliferation. Since increased biosynthesis of cell membranes is a part of tumor replication, choline transporter expression increases and choline kinase is upregulated [28]; subsequently, the uptake of ^{11}C -choline correlates with cancer metabolic rate [96].

Compared to ^{18}F -FDG, ^{11}C -choline PET/CT has higher avidity for prostate cancer cells, less background uptake and limited urinary excretion. Thus, ^{11}C -choline PET/CT may detect LR, LNM or DM. After RP, ^{11}C -choline PET/CT has a sensitivity of 38–85% and a specificity of 50–90% in detecting recurrence at all sites [35–42], with the highest accuracy in detecting LNMs [42]. After EBRT, ^{11}C -choline PET/CT has a sensitivity of 78–81% in detecting recurrence at all sites [41,43].

Unfortunately, ^{11}C -choline PET/CT sensitivity is dependent on cancer-specific variables (e.g., PSA levels, PSA kinetics and high-risk features [35–38,40,42,44–46]), and the presence of comorbid conditions (e.g., benign prostatic hyperplasia [97,98]). If PSA values are <1 ng/ml, ^{11}C -choline PET/CT has a low uptake in LNs, low accuracy in detecting disease, and therefore may not be recommended in planning LN target volumes [71]. Furthermore, ^{11}C -choline may have some uptake in the intestines. Although Scattoni *et al.* reported a high positive predictive value [37], a study by Schilling *et al.* found that three of ten patients with positive ^{11}C -choline PET scans had no tumor confirmed on pathology, supporting the need for histopathologic confirmation of positive PET findings [99]. Finally, due to the limited half-life of ^{11}C -choline, the use of this radioisotope is limited to centers with an onsite cyclotron.

Currently, ^{11}C -choline PET/CT is not recommended for detecting LR if PSA is <1 ng/ml [36] as MRI has higher sensitivity [37,42]. ^{11}C -choline PET/CT is useful to detect disease in the setting of BF and PSA >1 ng/ml after RP or EBRT, and to select specific patients for

tailored therapy. Patients with BF and ^{11}C -choline PET/CT scan that is positive for LR (but not LNM or DM) may be offered early salvage RT [37,71]. Patients with a ^{11}C -choline PET/CT scan that is positive for distal disease and short PSA-DT (e.g., <6 months), may be eligible for specific tailored therapy or enrollment in a clinical trial [37,71]; to complement, patients with LNM alone >1–2 years after initial RP may still benefit from salvage EBRT instead of systemic therapy [100]. Unfortunately, for many other patients (e.g., those with a scan suggestive of LNM but favorable PSA-DT and those with BF but PSA <1.0 ng/ml), ^{11}C -choline PET/CT scan cannot be used in clinical decision-making [35,38–39,44,99].

^{18}F -choline has cellular metabolism similar to that of ^{11}C -choline [89,101]. Similar to ^{11}C -choline, ^{18}F -choline metabolism is likely dependent on choline transporters and choline kinase activity [102]. The longer half-life of ^{18}F -choline versus ^{11}C -choline (110 vs 20 min) allows the radionuclide to be used in centers without a cyclotron. ^{18}F -choline has urinary elimination, which is a disadvantage for prostate cancer detection of LR; thus, it is not recommended for detection of suspected LR, since it seems to be less effective than MRI with endorectal coil [35]. After RP or EBRT, ^{18}F -choline PET/CT has a sensitivity of 47–92% in detecting LNM or DM [19,35,47–52]. ^{18}F -choline PET/CT has limited use in detecting distal disease (especially LNMs [51]) if PSA <4 ng/ml [49,52].

^{11}C -acetate—Fatty acid synthase, which uses acetate for the formation of fatty acids, has been shown to be overexpressed in prostate cancer [103]. Thus, ^{11}C -acetate PET/CT is theorized to have improved detection of LR, LNM or DM. After primary RP or EBRT, ^{11}C -acetate PET/CT has a reported sensitivity of 30–64% of detecting recurrence at any site [35,53–56]. ^{11}C -acetate appears to be more sensitive than ^{18}F -FDG PET/CT for the detection of LR [53,54]. Detection of DM with ^{11}C -acetate PET/CT has changed patient management in multiple studies [55,56].

Conversely, Fricke *et al.* report that ^{18}F -FDG PET/CT is more accurate than ^{11}C -acetate PET/CT for the detection distant disease [54]. ^{11}C -acetate PET/CT also seems to be PSA-dependent, as it detects LR in approximately half of patients with BF after RP when PSA is <1 ng/ml [35,55]. There is currently no recommendation for the use of ^{11}C -acetate PET/CT over MRI with endorectal coil in the detection of LR [35]. ^{18}F -acetate would theoretically be advantageous over ^{11}C -acetate in that it would not require an on-site cyclotron.

^{18}F -NaF

^{18}F -NaF is a positron-emitting, bone-seeking agent that is absorbed by the bone matrix, similar to $^{99\text{m}}\text{Tc}$ -MDP, reflecting blood flow and osteoblastic activity. ^{18}F -NaF was first approved in 1972, but it was eclipsed by $^{99\text{m}}\text{Tc}$ -MDP bone scans, and it made a resurgence in 2000. ^{18}F -NaF PET/CT has advantages over $^{99\text{m}}\text{Tc}$ -MDP bone scans, including increased spatial contrast and resolution; superior bone-to-background ratio; improved sensitivity and specificity; and faster whole-body scanning (up to 60 min after injection) [104]. Among men with BF after RP or EBRT, ^{18}F -NaF PET/CT is more useful than ^{18}F -FDG PET/CT in the detection of osseous metastases [105]; ^{18}F -NaF PET/CT sensitivity and specificity of detecting bone metastases have been reported to be 81–89% and 91–93%, respectively [47,57]. The probability of a positive scan correlates with PSA values [105].

Among patients with high-risk disease, ^{18}F -NaF PET/CT has a reported sensitivity of 20–81% and a specificity 93–100% for detecting bone metastases [57,104]. The disadvantages of ^{18}F -NaF include its accumulation in benign bone abnormalities (e.g., degenerative joint disease, and uncomplicated bone cysts, which are not seen on $^{99\text{m}}\text{Tc}$ -MDP scans [106]), detection of cancers other than those of the prostate, and inability to detect recurrence other than those of the bone.

$^{16}\beta$ - ^{18}F -fluoro-5 α -dihydrotestosterone

Androgen receptors may be a potential target of $^{16}\beta$ - ^{18}F -fluoro-5 α -dihydrotestosterone (^{18}F -FDHT) to detect metastatic disease [107]. Currently, no studies have assessed ^{18}F -FDHT PET/CT in the setting of BF. However, ^{18}F -FDHT has a sensitivity of 86% in prostate cancer patients with known metastases (either to bone or viscera); positive studies are associated with higher PSA levels [108].

Single amino acids— ^{11}C -methionine was one of the earliest investigated amino acid-based PET tracers for prostate cancer. ^{11}C -methionine has rapid uptake by tumor cells (peak ~10 min); its metabolism is related to amino acid transport and protein synthesis, correlating with tumor proliferation. ^{11}C -methionine is rapidly cleared from the blood pool by the liver and pancreas (without renal excretion), which theoretically makes it superior to ^{18}F -FDG in detection of prostate cancer LR [95]. Other radiolabeled amino acids that have potential for PET/CT-based detection of prostate cancer recurrence include tyrosine, phenylalanine, tryptophan, cysteine and leucine [109].

Novel prostate cancer-specific proteins—Bombesin (BBN) is a 14 amino acid neuropeptide that has a high affinity to the gastrin-releasing peptide receptor (GRPR). GRPR is expressed on the prostate cancer cell membranes, but not of benign hyperplastic prostate cells [109]. GRPR antagonists, which have been proposed to be better targeting agents than BBN agonists, have also been developed, including ^{18}F -fluorobenzoate-Lys³-BBN.

Integrins are transmembrane receptors that mediate attachment of a cell and its surroundings. Several $\alpha_v\beta_3$ integrin radionuclide tracers have been developed, including cilengitide and ^{18}F -galacto arginine–glycine–aspartate. Furthermore, a dual-receptor targeting of GRPR and $\alpha_v\beta_3$ is being investigated with ^{68}Ga -BBN and ^{18}F -arginine–glycine–aspartate peptide heterodimer. Novel protein targets are further reviewed by Beer *et al.* [89] and Hong *et al.* [109].

Conclusion & future perspective

The current commonly used imaging methods to detect prostate cancer recurrence are evolving from assessment of anatomical features to integration of functional and metabolic data. Specifically, MRI is being aided by multiparametric methods to detect changes in cellular metabolism, diffusion and blood flow. CT is being aided by PET and SPECT to detect metabolic processes and biomarkers associated with recurrent cancer. Finally, although not reviewed in detail in this article, the potential of MRI/PET for imaging patients with BF has been reported and appears promising [56]. Ongoing clinical trials that are

evaluating functional and metabolic imaging techniques to detect recurrent prostate cancer are listed in Table 4.

Compared with anatomic imaging techniques, functional and molecular imaging modalities have: increased variability in detecting recurrent cancer at particular disease sites (i.e., LR vs LNM vs DM); increased specificity for particular biomarkers; and decreased availability among hospitals. The effectiveness (i.e., efficacy compared with other imaging modalities) and the efficiency (i.e., the resource utilization) of functional and molecular imaging modalities have yet to be fully defined, particularly in larger studies [82].

Additionally, there are variations among the use of functional and molecular imaging techniques around the world. For example, fluoro/choline PET has gained marketing approval in several European countries and ^{11}C -choline PET has cleared US FDA approval for use in the Mayo Clinic in the USA. With respect to ongoing clinical trials (Table 4), the trial with that encompasses the greatest number of centers around the world is NCT01667536, a Phase 2 study of $^{99\text{m}}\text{Tc}$ -MIP-1404 in men with high-risk prostate cancer scheduled for RP with extended pelvic lymph node dissection [111]. The investigational agent, $^{99\text{m}}\text{Tc}$ -MIP-1404, is a small molecule that targets PSMA. The primary outcome measure will be to detect prostate cancer within the prostate gland, tissue distribution of the drug, and safety of the agent. Given the variations of use and availability of imaging modalities around the world, the AUA and ASTRO state that overall, the decision regarding which modality to use to determine presence or absence of recurrent disease will depend on the availability of specific modalities and the clinician's goals of imaging [84].

With respect to multiparametric MRI, large randomized studies demonstrating efficacy of various MRI multiparametric studies sequences have yet to be performed. Future investigations will help to differentiate between recurrence and benign processes. Next, they will aid in decision-making in patients with positive study with an elevated PSA, but otherwise negative workup. Additionally, they will define specific patient subpopulations (e.g., high-risk patients and/or patients with suspected LNM) that should be imaged with a particular multiparametric modality. The generation of clinically useful PET and SPECT tracers will depend on the consideration of various factors. First, the isotope used is important, as short half-life isotopes (e.g., ^{18}F) are more suitable for peptide and amino acid labeling, while long half-life isotopes (e.g., ^{111}In and ^{74}As) are more suitable for antibody labeling. Notably, short half-life isotopes may be limited to hospitals with onsite cyclotrons. Second, the tracer should have a high metabolic stability and preferentially seek non-naturally occurring targets characteristic of prostate cancer cells to increase their specificity. Third, tracers must have suitable pharmacokinetic properties (e.g., rapid blood clearance and minimal urinary excretion), low nonspecific accumulation in normal tissues (e.g., the gut and fat tissues). Future approaches to RIS may involve antibody fragments (e.g., diabodies and minibodies) [109]. Current antibodies used in RIS are produced in mice. Murine IgGs are recognized as foreign proteins in humans, leading to the development of human antimurine antibodies, limiting the accuracy of RIS. Finally, other intracellular pathways (e.g., purine and pyrimidine synthesis) correlating to cellular metabolism may be used.

Just as our understanding of cancer genomics and proteomics has added complexity to the landscape of potential therapeutic approaches, we envision future selection of imaging studies will be individualized based on tumor characteristics. The tumor grade, molecular markers, or gene expression signatures identified in a patient's tumor biopsy may guide clinicians toward a particular imaging approach – metabolic versus antibody-specific – to identify recurrence. In this fashion, future guidelines and recurrence detection paradigms may rely more upon biomarker-defined tumor characteristics than other traditional clinical factors such as PSA level, Gleason score and pathological stage.

The diagnostic capabilities of imaging technology may be complemented by therapeutic interventions; for example, high intensity focused ultrasound therapy is a novel technology used for the treatment of bone metastases, and it may be performed with either ultrasound or magnetic resonance guidance. Focused ultrasound therapy improves pain and quality of life for patients with painful bone metastases who are not candidates for RT [112]. The capabilities of multiparametric MRI may be combined with focused ultrasound therapy to create a joint diagnostic–therapeutic imaging modality. Furthermore, the antibodies against prostate cancer-specific epitopes (e.g., J591) could be linked to novel radionuclides; for example, α -emitting radioisotopes, which are a promising therapy for prostate cancer bone metastases [113], may be linked to diagnostic antibodies.

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Box 1. Population, intervention, control, outcome, study design inclusion criteria.

Population

- Men with localized (T_1 – T_2 , N_0 – N_x , M_0) and locally advanced (T_3 – T_4 , N_0 – N_x , M_0) prostate cancer status post treatment with EBRT or RP

Intervention

- Use of novel imaging modality, including multiparametric MRI or ET, to detect prostate cancer recurrence

Control

- Either no control group (i.e., detection of recurrence with imaging modality alone) or a multiarm study that contains the novel imaging modality

Outcomes: efficacy

- Clinical (surrogate outcomes) for all studies: sensitivity and/or specificity
- Patient and study-specific: detection of LR, LNM and DM; dependence on PSA

Study design: efficacy

- Retrospective and prospective studies, any number of patients, with one or more arms

DM: Distant metastasis; EBRT: External beam radiation therapy; ET: Emission tomography; LNM: Lymph node metastasis; LR: Local recurrence; PSA: Prostate-specific antigen; RP: Radical prostatectomy.

EXECUTIVE SUMMARY

Necessity of imaging in the setting after treatment for prostate cancer

- Accurate detection of recurrent disease is important because it allows for appropriate treatment selection (e.g., local vs systemic therapy) and early delivery (e.g., salvage external beam radiation therapy), which favor patient outcome.
- As of 2013, most models for detecting recurrent prostate cancer depend on pretreatment characteristics, including prostate-specific antigen (PSA), Gleason score and T-stage.

Role of anatomic imaging in detection of recurrent prostate cancer

- Traditional imaging modalities to evaluate recurrent disease include the following: radionuclide skeletal scintigraphy ('bone scan'); transrectal ultrasound-guided biopsy; CT scan; and MRI.
- In general, these techniques may detect macroscopic disease, but they have poor sensitivity for very low volume disease, or when PSA is <10 ng/ml. The National Comprehensive Cancer Network has no clear recommendations for imaging in biochemical failure after radical prostatectomy. The National Comprehensive Cancer Network recommends a biopsy and bone scan for certain men who are candidates for local therapy in biochemical failure after external beam radiation therapy. The European Association of Urology similarly states that routine imaging of stable patients is not recommended. The American Urologic Association and American Society for Radiation Oncology caution clinicians that the yield of some modalities (e.g., bone scan) is extremely low in patients with PSA values <10 ng/ml.

Role of functional & molecular imaging in detection of recurrent prostate cancer

- In contrast to conventional morphological imaging, functional and molecular imaging is focused on the molecular and cellular characteristics of individual tumors and the surrounding tissues.
- Functional imaging
- Multiparametric MRI techniques currently under investigation include magnetic resonance spectroscopy, dynamic contrast-enhanced MRI, diffusion-weighted MRI and lymphotropic nanoparticle MRI.
- Molecular imaging
- Radionuclide-based techniques under investigation include radioimmunoscinigraphy (e.g., ¹¹¹In-capromab pendetide); small molecules (e.g., ¹⁸F-fluorodeoxyglucose, ¹¹C-choline, ¹⁸F-choline, ¹¹C-acetate, ¹⁸F-acetate, ¹⁸F-NaF and ¹⁸F-FDHT); amino acids (e.g., ¹¹C-methionine); and protein-specific molecules (e.g., bombesin derivatives).

Future perspective on functional & molecular imaging techniques

- Compared with anatomic imaging techniques, functional and molecular imaging modalities have: increased variability in detecting recurrent cancer at particular disease sites; increased specificity for particular biomarkers; and decreased availability among hospitals.
- The effectiveness (i.e., efficacy compared with other imaging modalities) and the efficiency (i.e., the resource utilization) of novel imaging modalities have yet to be fully defined.

Figure 1. Preferred reporting items for systematic reviews and meta-analyses literature selection process.

CT: Computed tomography; SPECT: Single-photon emission computed tomography.

Figure 2. Novel radiotracers used in the detection of recurrent prostate cancer.

Novel radiolabeled PET tracers (blue boxes) are used in the detection of metabolic processes (orange boxes) and expressed proteins (purple boxes) of prostate cancer cells. 5P: 5-phosphate; α-KG: α-ketoglutarate; AA: Amino acid; AR: Androgen receptor; BBN: Bombesin; C: Carbon; CoA: Coenzyme A; DOTA: 1,4,7,10-tetraazadodecane-N,N',N'',N'''-tetraacetic acid; FB: Fluorobenzoate; FDHT: Fluoro-5α-dihydrotestosterone; G6P: Glucose-6-phosphate; mAb: Monoclonal antibody; RGD: Arginine–glycine–aspartate; SAM: S-adenosyl methionine. For color image, please see www.futuremedicine.com/doi/full/10.2217/fon.13.196

Table 1.

Guidelines for the use of common imaging modalities to detect prostate cancer recurrence.

Modality	General comments for either setting	Post-EBRT	Post-RP
^{99m} Tc-MDP, bone scan	Noninvasive Detects DM (bones) only High sensitivity, low specificity	Recommended in certain men who are candidates for local therapy [60]	Commonly performed Positive scan may be predicted with nomogram [61] Relative indications [9]: PSA-DT <6 min; PSA velocity >0.5 ng/ml/month; absolute baseline PSA >10 ng/ml; symptoms of bone disease
TRUS-guided biopsy	Invasive Operator-dependent Detects LR only Low sensitivity, low specificity	Recommended in certain men who are candidates for local therapy [60]	Not routinely recommended [9,60] Color/power-Doppler may improve distinction between recurrence and fibrosis [62,63]
Abdomen/pelvis CT	Noninvasive Detects DM, LNM and >LR	Not routinely recommended [9,60]	Not routinely recommended Scar tissue may be confused with LR [9] Not recommended, although it may be used for defining salvage EBRT target volumes [64]
Conventional T ₁ /T ₂ w MRI alone ± endorectal coil	Noninvasive Detects LR, LNM and DM Specific but not sensitive for LNM Most sensitive technique in detection of DM	T ₁ /T ₂ w MRI alone [58] or with endorectal coil [65] is limited because contrast between benign irradiated tissues and recurrence cancer is decreased, making detection more difficult Endorectal coil may exacerbate rectal toxicity [58]	Recommended if high risk of LR [9]: positive SMs; ECE; SV involvement MRI may be used for defining salvage EBRT target volumes [66] Endorectal coil increases sensitivity and specificity of finding LR to >95%, improves target volume definition [67]

BF: Biochemical failure; CT: Computed tomography; DM: Distant metastasis; EBRT: External beam radiation therapy; ECE: Extracapsular extension; LNM: Lymph node metastasis; LR: Local recurrence; PSA-DT: Prostate-specific antigen doubling time; RP: Radical prostatectomy; RT: Radiation therapy; SM: Surgical margin; SV: Seminal vesicle; T₁/T₂w: T₁/T₂ weighted; TRUS: Transrectal ultrasound.

Table 2.

Future imaging modalities that may detect prostate cancer recurrence and its source.

Modality	Detection of recurrence		References for published data after primary therapy		PSA – independence		Potential in detecting disease	
	Sensitivity (%)	Specificity (%)	EBRT	RP	LR	LNM	DM	
Multiparametric MRI								
MRS	56–89	78–88	[12,13]	[14,15]	NR	+	NR	
DCE	71–92	75–100	[16]	[14,17–19]	NR	+	NR	
DW	62	97	[20]	[21]	NR	+	NR	
LTNP	NR	NR	[22]	NR	NR	–	–	
RIS SPECT								
¹¹¹ In-capromab pendetide (ProstaScint™, Cytogen Corporation, NJ, USA)	75–86	47–86	[23–28]	[27]	+	+	+/–	
¹¹¹ In- or ¹⁷⁷ Lu-1591	98	N/A	[29,30]	[29,30]	+	+	+	
Small-molecule PET								
¹⁸ F-FDG	50–80	72–100	[31–34]	[31–33]	–	+/–	+	
¹¹ C-choline	38–98	50–100	[35–42]	[41,43–46]	–	+	+	
¹⁸ F-choline	47–92	33–99	[35,47–52]	[19,47–49]	–	+/–	+	
¹¹ C-acetate	30–64	NR	[35,53–56]	[53,54]	–	+	+	
¹⁸ F-NaF	81–89	91–93	[47]	[47,57]	–	–	+	
¹⁸ F-FDHT	NR	NR	NR	NR	–	–	+	
Single AA PET								
¹¹ C-methionine	NR	NR	NR	NR	–	+	+	

+: Likely useful; +/-: Equivocal data; -: Likely not useful; AA: Amino acid; CT: Computed tomography; DCE: Dynamic contrast enhanced; DM: Distant metastasis; DW: Diffusion weighted; EBRT: External beam radiation therapy; FDG: Fluorodeoxyglucose; FDHT: Fluoro-5 α -dihydrotestosterone; LNM: Lymph node metastasis; LR: Local recurrence; LTNP: Lymphotropic nanoparticle; MRS: Magnetic resonance spectroscopy; NR: Not reported; PSA: Prostate-specific antigen; PSMA: Prostate-specific membrane antigen; RIS: Radioimmunoscintigraphy; RP: Radical prostatectomy; SPECT: Single-photon emission tomography; TRUS: Transrectal ultrasound.

Table 3.

Radionuclide characteristics.

Radionuclide	Need for cyclotron	$t_{1/2}$	Metabolic process measured	Excretion	SPECT or PET/CT
^{99m}Tc -MDP	No	6 h	Osteoblastic activity	NA	SPECT
^{111}In -capromab pendetide	No	2–8 days	mAb anti-intracellular PSMA epitope	NA	SPECT
^{111}In - or ^{177}Lu -J591	No	3 days	mAb anti-extracellular PSMA epitope	NA	SPECT
^{18}F -FDG	<2 h away	110 min	Glucose metabolism	Renal	PET/CT
^{11}C -choline	On-site	20 min	Cell membrane synthesis	Hepatic	PET/CT
^{18}F -choline	<2 h away	110 min	Cell membrane synthesis	Renal	PET/CT
^{11}C -acetate	On-site	20 min	Lipid synthesis	Hepatic	PET/CT
^{18}F -acetate	<2 h away	110 min	Lipid synthesis	Renal	PET/CT
^{18}F -NaF	<2 h away	110 min	Osteal blood flow, osteoblastic activity	Hepatic	PET/CT
^{18}F -FDHT	<2 h away	110 min	AR expression	NA	PET/CT
^{11}C -methionine	On-site	20 min	Amino acid transport, protein synthesis	Hepatic	PET/CT
^{11}C or ^{18}F -AAs	Depends	Depends	Amino acid transport, protein synthesis	Depends	Depends
BBN derivatives	Depends	Depends	GRPR agonists and antagonists	Depends	Depends

AA: Amino acid; AR: Androgen receptor; BBN: Bombesin; CT: Computed tomography; FDG: Fluorodeoxyglucose; FDHT: Fluoro-5 α -dihydrotestosterone; GRPR: Gastrin-releasing peptide receptor; HDP: Hydroxymethyl diphosphonate; mAb: Monoclonal antibody; MDP: Methyl diphosphonate; NA: Not applicable; PSMA: Prostate-specific membrane antigen; SPECT: Single-photon emission computed tomography.

Ongoing clinical trials of functional and molecular imaging techniques for the detection of recurrent prostate cancer.

Type	Name/Identifier [†]	Phase or study type and design	Postprimary therapy	Imaging technique	Center (location)	Target (n)	Primary outcomes
Molecular	NCT00963755	Prospective, cohort	RP	¹⁸ F-choline PET/CT	University of Lausanne Hospitals (Lausanne, Switzerland)	60	Impact for resaging and localizing relapse compared with standard clinical workup
Molecular	NCT01808222	II	Non-RP	Anti-3- ¹⁸ F-FACBC PET/CT	Emory University (GA, USA)	25	Presence of cancer tissue inside and outside of the prostate bed, confirmed by MRI and biopsy
Molecular	NCT01566808	II	RP	Anti-3- ¹⁸ F-FACBC PET/CT	Emory University	162	Failure-free survival; to improve selection and outcomes of patients receiving post-RP RT
Molecular	NCT01304485	II	RP or RT	¹¹ C-acetate PET/CT	Arizona Molecular Imaging Center (AZ, USA)	500	Standardized uptake value
Molecular	NCT01173146	II	RP	ProstaFluor® (Spectros Corporation, CA, USA) a PSMA-targeted fluorescent agent, PET/CT	Vanderbilt University (TN, USA), Cornell University (NY, USA)	96	Efficacy, as measured by positive scan and margin positivity after surgery
Molecular	NCT01186601	I	NS, includes other cancers	BAY94-9392, a ¹⁸ F-labeld glutamate derivative PET/CT	Stanford University (CA, USA)	30	Accumulation of BAY94-9392 in primary cancer lesions confirmed by histology, LR and DM
Molecular	NCT01417182	I	NS, includes advanced disease	¹⁸ F-benzyl-L-cysteine, a PSMA-targeted low-molecular-weight antige PET/CT	Johns Hopkins University (MD, USA)	10	Biodistribution and safety
Molecular	NCT01667536	II	NA, scheduled for RP and extended pelvic lymph node dissection	^{99m} Tc-MIP-1404, a small molecule that targets PSMA, PET/CT	USA; Belgium; Czech Republic; Hungary; Italy; The Netherlands; Poland; Russia	100	Ability of ^{99m} Tc-MIP-1404 to detect prostate cancer within the prostate gland; tissue distribution of the drug; and safety
Molecular and functional	NCT01804231	Prospective, singlegroup intervention	RP	¹⁸ F-choline PET/MRI fusion	Lawson Health Research Institute (London, Canada)	40	Frequency of change in clinical management of patients based on questionnaires provided to investigators before and after scan
Functional	NCT01607008	Interventional, single group	RT	Multiparametric MRI, including MRS, DW and DCE	Johns Hopkins University	20	Predicting treatment response, defined by anatomical, functional, and lociton changes
Functional	NCT01834001	Observational, prospective	RT	Multiparametric MRI, unspecified subtypes	National Cancer Institute (MD, USA)	190	Determine LR rate using standard biopsies

[†]Please see ClinicalTrials.gov for more details [110].

Anti-3-¹⁸F-FACBC: Anti-1-amino-3-¹⁸F-cyclobutane-1-carboxylic acid; CT: Computed tomography; DCE: Dynamic contrast enhanced; DM: Distant metastasis; DW: Diffusion weighted; LR: Local recurrence; MRS: Magnetic resonance spectroscopy; NA: Not applicable; NS: Not specified; PSMA: Prostate-specific membrane antigen; RP: Radical prostatectomy; RT: Radiotherapy.