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Abstract

Purpose—This paper provides a review on molecular imaging with positron emission tomography (PET) and magnetic resonance imaging (MRI) for prostate cancer detection and its applications in fusion targeted biopsy of the prostate.

Methods—Literature search was performed through the PubMed database using the keywords “prostate cancer”, “MRI/ultrasound fusion”, “molecular imaging”, and “targeted biopsy”. Estimates in autopsy studies indicate that 50% of men older than 50 years of age have prostate cancer. Systematic transrectal ultrasound (TRUS) guided prostate biopsy is considered the standard method for prostate cancer detection and has a significant sampling error and a low sensitivity. Molecular imaging technology and new biopsy approaches are emerging to improve the detection of prostate cancer.

Results—Molecular imaging with PET and MRI shows promising results in the early detection of prostate cancer. MRI/TRUS fusion targeted biopsy has become a new clinical standard for the diagnosis of prostate cancer. PET molecular image-directed, three-dimensional ultrasound-guided biopsy is a new technology that has great potential for improving prostate cancer detection rate and for distinguishing aggressive prostate cancer from indolent disease.

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Compliance with ethical standards

Ethical statement

The study was approved by the IRB of Emory University.

Conflict of interest

The authors have participated in sponsored research involving ^{18}F-fluciclovine among other radiotracers. Emory University is eligible to receive royalties for ^{18}F-fluciclovine.

Conclusion—Molecular imaging and fusion targeted biopsy are active research areas in prostate cancer research.

Keywords

Prostate cancer; Targeted biopsy; Molecular imaging; Positron emission tomography (PET); Magnetic resonance imaging (MRI); Image segmentation; Image registration

Introduction

Estimates in autopsy studies indicate that 50% of men older than 50 years of age have prostate cancer [1, 2]. In 2015, 220,800 American men were diagnosed with prostate cancer [3]. Systematic transrectal ultrasound (TRUS) guided prostate biopsy is considered the standard method for prostate cancer detection. The current 12-core template biopsy technique has a significant sampling error and a low sensitivity (24–52%) [4–7], and it can miss up to 30% of cancers [8]. As a result, a patient may have a "negative" biopsy, but may, in fact, be harboring an occult cancer. Alternatively, a diagnosis of cancer may have been made, but the patient is under-staged, because the most aggressive histologic region of the tumor has not been sampled. Because of these limitations, patient management may not be optimized.

Because of the limitations of the current biopsy approach, it is a difficult challenge for physicians to manage patients with false negative biopsies who, in fact, harbor curable prostate cancer as indicated by biochemical measurements, such as rising prostate-specific antigen (PSA). Another important challenge facing physicians is patients diagnosed on biopsy as having premalignant lesions, i.e., multifocal high-grade prostatic intraepithelial neoplasia, and, in particular, atypical small acinar proliferation (ASAP). This biopsy result is clinically significant as there is a 40–80% chance of finding cancer on repeat biopsy if there is ASAP [9]. For ASAP patients, it is vital to re-biopsy the same area. Finally, for those patients, increasing in number, who have selected active surveillance for management of prostate cancer, it is vital to be able to reliably biopsy the same cancer foci over time to ensure that these areas are not becoming de-differentiated, a finding which would move patients to be treated with definitive local therapy. Unfortunately, the current two-dimensional (2D) ultrasound provides only an imprecise localization of the abnormal findings, and it is not possible to be certain that the same area has been sampled by the repeat biopsy. Because of the limitations and uncertainty associated with the current approach, both the patient and physician face significant challenges in making treatment decisions.

Molecular imaging and new targeted biopsy technology have been developed to improve the cancer detection rate from the current standard of care practice. Magnetic resonance imaging (MRI)/TRUS fusion targeted biopsy represents a new technique to improve cancer detection rate [10–14]. Patients who are eligible for active surveillance (AS) on their initial diagnostic biopsy often receive an MRI as well as a confirmatory biopsy [15, 16]. The suspicion level on MRI correlates with likelihood of detection of high-grade prostate cancer [10, 17–19]. TRUS saturation biopsy has also been used to monitor patients on AS, but can have

significant morbidity [20]. Positron emission tomography (PET) can detect metabolic and functional aspects of cancer. Various PET tracers have been developed for prostate cancer imaging. In this review, we will focus on MRI/TRUS fusion targeted biopsy and PET molecular imaging directed, 3D ultrasound-guided biopsy of the prostate. Literature search was performed through the PubMed database using the keywords “prostate cancer”, “MRI/ultrasound fusion”, “molecular imaging”, and “targeted biopsy”. We selected the papers published in English between January 1, 2010 and April 1, 2016.

Multiparametric MRI for the prostate

MR imaging provides excellent soft-tissue contrast and has been increasingly used for the detection of prostate tumors. As shown in Fig. 1, multiparametric MRI (mp-MRI) includes T2-weighted (T2W) MRI, diffusion-weighted imaging (DWI), dynamic contrast-enhanced imaging (DCE-MR), and MR spectroscopy (MRS). The mp-MRI has proven to be an effective technique to localize high-risk prostate cancer [21, 22]. The combined use of anatomic and functional information provided by the multiparametric approach increases the accuracy of MR imaging in detecting and staging prostate cancer [21, 22]. The European Society of Urogenital Radiology (ESUR) in 2012 established the Prostate Imaging-Reporting and Data System (PI-RADS) scoring system for multiparametric MRI of the prostate [23]. The MR PI-RADS aims to enable consistent interpretation, communication, and reporting of prostate mp-MRI findings [23, 24].

Contemporary MR imaging of the prostate combines anatomic images from high-resolution T1W and T2W sequences and functional information obtained from DWI, DCEI, and MRS. The PI-RADS Prostate MR Guidelines published in 2012 suggest the use of T2W images plus 2 functional techniques [23]. The prostate anatomy is visualized with T2W images; DWI and MRS add specificity to lesion identification, while DCE-MRI has a high sensitivity in cancer detection. In the PI-RADS™ v2, the essential components of the mp-MRI prostate examination are T2W, DWI, and DCE [25]. A combination of anatomical and functional imaging is necessary to obtain high and stable accuracy in clinical practice. Below, we focus on three MR sequences that are mostly frequently used in prostate imaging.

T2-weighted MRI

The acquisition of high-resolution T2W images of the prostate is the first step in an mp-MR imaging protocol. In T2W images, the peripheral zone of the prostate has hyperintense signal, whereas the central and transition zones have low signal, allowing the zonal anatomy of the prostate to be clearly delineated. In T2W images, prostate cancer in the peripheral zone is usually depicted as a low-signal area. However, the growth pattern and the aggressiveness of the tumor can alter its appearance. T2W MR imaging has been advocated as an accurate technique in the detection of prostate cancer in the transition zone [26, 27]. In T2W MR images, the tumor region of interest has more dark pixels than bright pixels, whereas the normal tissue has more bright pixels than dark pixels. Different features, including fractal features, textural features, and signal intensity, can be used to aid in the detection of suspicious lesions. Prostate cancers at the central gland and peripheral zone usually have significantly different textures on T2W MR images [28].

Diffusion-weighted MRI

The diffusion properties of tissue are related to the amount of interstitial free water and permeability. In general, cancer tends to have more restricted diffusion than normal tissue, because of the higher cell densities and abundance of intra- and inter-cellular membranes in cancer [29]. Diffusion-weighted MRI images can be used to detect prostate cancer from differences in the diffusion of water molecules of the normal and tumor tissues [29]. The diffusion-weighted image is usually generated with different b values which can be used to calculate the apparent diffusion coefficient (ADC), and the ADC for each pixel of the image is displayed as ADC map. Diffusion of water molecules in tumor tissue is thought to reflect tissue architecture, such as cell density and nucleus/cytoplasm ratio, and reductions in ADC values. For these reasons, ADC values have received the attention as a predictor of Gleason score in prostate cancer [30, 31]. Studies show that DWI findings may indicate tumor aggressiveness [32–34]. DWI images and ADC maps are the key component of the prostate mp-MRI exam. For example, the combination of 10th percentile ADC, average ADC, and T2-weighted skewness is promising in the differentiation of prostate cancer from normal tissue [34].

Dynamic contrast-enhanced MRI

DCE-MRI, which enables visualization of vascular permeability and perfusion, is an important tool in oncology to define tumor. DCE-MRI is sensitive to alterations in vascular permeability, extracellular space, and blood flow. The clinical application of DCE-MRI for prostate cancer is based on data showing that malignant lesions show earlier and faster enhancement and earlier contrast agent washout compared with healthy prostate tissues [35]. DCE-MRI data can be analyzed with various semiquantitative or quantitative models to extract parameters related to vascular permeability, extracellular space, blood flow, and water exchange [36]. The most commonly used quantitative approach of analyzing DCE-MRI is two-compartment pharmacokinetic (PK) models that can be used to generate pharmacokinetic parameters, such as Ktrans (transfer of gadolinium contrast from the vasculature to the tumor, representing forward vascular perfusion and permeability) and Kep (reverse transfer of contrast agent from the extracellular space back to the plasma, representing backward leakage) to quantify tumor enhancement and the contrast uptake and washout [37]. DCE-MRI usually has lower spatial resolution than other sequences, especially when DCE-MRI is performed rapidly in a short period of time.

Magnetic resonance spectroscopy (MRS)

Magnetic resonance spectroscopy (MRS) is an MR technique for characterization of chemical composition in tissue. The position of each metabolite peak in the output graph reflects the resonant frequencies or chemical shifts of its hydrogen protons, and the area of each peak reflects the relative concentration of that metabolite [123]. On MRS, the resonances for the prostate metabolites, such as citrate (Cit), creatine (Cre), and choline (Cho), occur at distinct frequencies (2.60, 3.04, and 3.20 ppm for Cit, Cre, and Cho, respectively). In vivo MRS can be used for metabolite profiling in the prostate tissue to discriminate carcinomas and healthy prostate. The healthy prostate produces a high level of citrate. In prostate cancer tissue, citrate levels decrease markedly. Prostate cancer also leads

to choline increased. The metabolite ratios, such as Cho/Cit, (Cho + Cre)/Cit are significant to discriminate between prostate cancer and benign prostatic hyperplasia. The ratio of choline to citrate (Cho/Cit) is increased in cancer. The choline plus creatine to citrate ratio ([Cho + Cre]/Cit) has widely been studied and cut-off values have been suggested for the detection of prostate cancer.

MRI/TRUS fusion targeted biopsy

As the current standard of care practice for an initial prostate biopsy has a low cancer detection rate, the development and evaluation of new biopsy technology are active research areas [7, 38–51]. It has been reported that MR/TRUS fusion biopsy detects more cancer per core than standard 12-core TRUS biopsy [38]. The use of 3D tracking and image fusion has the potential to improve current methods for diagnosis and follow-up of prostate cancer [41–44].

Pinto and co-workers reported various studies on MR/TRUS fusion targeted biopsy [38–40, 52]. In a landmark prospective cohort study of 1003 men undergoing both targeted and standard biopsy concurrently from 2007 through 2014 at the National Cancer Institute (NIH) in the United States [52], targeted vs standard biopsy and the two approaches combined were assessed for the diagnosis of intermediate- to high-risk prostate cancer. Patients were referred for elevated level of PSA or abnormal digital rectal examination results, often with prior negative biopsy results. Risk categorization was compared among targeted and standard biopsy and, when available, whole-gland pathology after prostatectomy as the “gold standard”. Patients underwent mp-MRI to identify regions of prostate cancer suspicion followed by targeted MRI/TRUS fusion biopsy and concurrent standard biopsy. The primary objective was to compare targeted and standard biopsy approaches for detection of high-risk prostate cancer (Gleason score ≥ 4 + 3); secondary end points focused on detection of low-risk prostate cancer (Gleason score 3 + 3 or low-volume 3 + 4) and the biopsy ability to predict whole-gland pathology at prostatectomy. The study results show that targeted MRI/TRUS fusion biopsy diagnosed 461 prostate cancer cases, and standard biopsy diagnosed 469 cases. There was exact agreement between targeted and standard biopsy in 690 men (69%) undergoing biopsy. Targeted biopsy diagnosed 30% more high-risk cancers vs standard biopsy (173 vs 122 cases, $P < .001$) and 17% fewer low-risk cancers (213 vs 258 cases, $P < .001$). When standard biopsy cores were combined with the targeted approach, additional 103 cases (22%) of mostly low-risk prostate cancer were diagnosed (83% low risk, 12% intermediate risk, and 5% high risk). The predictive ability of targeted biopsy for differentiating low-risk from intermediate- and high-risk disease in 170 men with whole-gland pathology after prostatectomy was greater than that of standard biopsy or the 2 approaches combined (area under the curve, 0.73, 0.59, and 0.67, respectively; $P < .05$ for all comparisons). Among men undergoing biopsy for suspected prostate cancer, targeted MR/ultrasound fusion biopsy, compared with standard extended-sextant ultrasound-guided biopsy, was associated with increased detection of high-risk prostate cancer and decreased detection of low-risk prostate cancer. Future studies will be needed to assess the ultimate clinical implications of targeted biopsy.

Marks and colleagues have also published various studies on MR/TRUS fusion biopsy [53–56] and found that when suspicious lesions were targeted by MR/TRUS fusion, the positive biopsy rate per core is higher (33%) than that (7%) of the standard, systematic biopsy [45, 53, 54, 56–60], In men with prior negative biopsy and elevated PSA, fusion targeted biopsy revealed prostate cancer in 34% [56]. Marks and colleagues used an Artemis system (Eigen, Grass Valley, CA), a commercially available robot-like device that can interface with any OEM ultrasound machine to provide 3D navigation and recording for prostate biopsies. The device has the capability to plan targets for biopsy within the prostate. It has predefined biopsy plans, like the systematic 12-core plan and custom plans, as defined by the urologist. The device also has the capability to load the previous biopsy plans for re-biopsy. In addition, together with the ProFuse software package which allows a radiologist to annotate suspicious areas on mp-MRI using advanced visualization tools, Artemis is capable of mapping suspicious areas from MRI to TRUS for biopsy using MR/TRUS fusion. During biopsy, the user is able to navigate to these areas through a visual interface that shows the real-time position of the probe in multiple views (Table 1).

Molecular imaging with PET for the prostate

Positron emission tomography (PET) can detect metabolic and functional information of cancer and various PET imaging agents are under development and validation for prostate cancer detection. The ^{68}Ga-labed small-molecule inhibitor Glu-NH-CO–NH-Lys(Ahx)-HBED-CC is a new PET tracer that has been investigated for prostate cancer detection in the Europe [61–64]. PET/CT with ^{68}Ga-Prostate-Specific Membrane Antigen (PSMA) ligand shows substantially high detection rates [63]. Other PET tracers include ^{11}C-choline [65–68], ^{18}F-fluorocholine [69–71], ^{11}C-acetate [72–75], radiolabeled minibody [76], 2-^{18}F-fluoropropionic acid (^{18}F-FPA) [77], ^{18}F 16-beta-fluoro-5-alpha-dihydrotestosterone (^{18}F-FDHT) [78], radiolabeled J591 [79–81], ^{11}C-methionine [82–84], *N*-[*N*-[(*S*)-1,3-di-carboxypropyl]carbamoyl]-4-[^{18}F]fluorobenzyl-L-cysteine (^{18}F-DCFBC) [85, 86], and etc. It has been reported that ^{18}F-DCFBC PET was able to detect more clinically significant high-grade and larger-volume tumors with higher specificity than MR imaging [87]. PET imaging with ^{11}C-choline [67, 88] has been approved by the U.S. Food and Drug Administration (FDA) for prostate cancer detection and staging. PET imaging with new molecular imaging tracers, such as anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid (^{18}F fluciclovine), has shown promising results for detecting and localizing prostate cancer in humans [89, 90]. Fluciclovine (Axumin, Blue Earth Diagnostics, UK) was originally developed at Emory University and was recently approved by the U.S. FDA for detection of recurrent prostate cancer.

Fluciclovine PET molecular imaging of prostate cancer

Fluciclovine is a synthetic L-leucine analog that has been developed for detecting and staging prostate cancer with PET [91]. In a prospective study of 93 patients, Schuster et al. reported the results of fluciclovine PET imaging in recurrent prostate cancer [92]. A total of 93 patients underwent fluciclovine PET-CT plus ^{111}In-capromab pendetide single photon emission computerized tomography–computerized tomography for suspected recurrent prostate carcinoma within 90 days. In the 91 of 93 patients with sufficient data for a

consensus on the presence or absence of prostate/bed disease fluciclovine had 90.2% sensitivity, 40.0% specificity, 73.6% accuracy, 75.3% positive predictive value, and 66.7% negative predictive value compared to ^{111}Indium-capromab pendetide with 67.2, 56.7, 63.7, 75.9, and 45.9%, respectively. In the 70 of 93 patients with a consensus on the presence or absence of extraprostatic disease, fluciclovine had 55.0% sensitivity, 96.7% specificity, 72.9% accuracy, 95.7% positive predictive value, and 61.7% negative predictive value compared to ^{111}Indium-capromab pendetide with 10.0, 86.7, 42.9, 50.0, and 41.9%, respectively. Of 77 index lesions used to prove positivity histological proof was obtained in 74 (96.1%). Fluciclovine identified 14 more positive prostate bed recurrences (55 vs 41) and 18 more patients with extraprostatic involvement (22 vs 4). Fluciclovine positron emission tomography/computerized tomography correctly up-staged 18 of 70 cases (25.7%) in which there was a consensus on the presence or absence of extraprostatic involvement.

Schuster et al. also reported the correlation of fluciclovine PET images with histologic examination of the surgically removed prostate [93]. The study was also to determine if uptake correlates to markers of tumor aggressiveness, such as Gleason score. Ten patients with prostate carcinoma pre-radical prostatectomy underwent 45 min dynamic PET-CT of the pelvis after IV injection of 347.8 ± 81.4 MBq fluciclovine. Each prostate was co-registered to a separately acquired MR, divided into 12 sextants, and analyzed visually for abnormal focal uptake. Highest combined sensitivity and specificity were 81.3 and 50.0%, respectively. SUVmax was significantly higher ($P < .05$) for malignant sextants compared with non-malignant sextants, though there was overlap of activity between malignant and non-malignant sextants. SUVmax also significantly correlated ($P < .05$) with Gleason score. It is concluded that while not possessing sufficient specificity for planning of radiation therapy to the prostate, fluciclovine PET may be useful to guide biopsy to the most aggressive lesion.

Imaging with fluciclovine succeeded in identifying both primary and metastatic prostate carcinoma on the initial staging as well as uptake in recurrent prostate carcinoma within the prostate bed, lymph nodes, and bone [89]. In a study by Turkbey and colleagues [94], fluciclovine PET/CT shows higher uptake in intraprostatic tumor foci than in normal prostate tissue; however, fluciclovine uptake in tumors is similar to that in benign prostatic hyperplasia (BPH) nodules. Combined fluciclovine PET/CT and T2-weighted MR imaging enable more accurate localization of prostate cancer lesions than either modality alone [94]. PET/CT with fluciclovine shows focal uptake at the tumor and thus can provide location information to direct targeted biopsy of the prostate [93]. By combining PET/CT with 3D ultrasound images, multimodality image-guided targeted biopsy has become a promising technology for improved detection and diagnosis of prostate cancer [95].

PSMA ligand PET imaging of prostate cancer

Prostate-specific membrane antigen (PSMA) is a type II integral membrane glycoprotein, which is considered to be a well-established target antigen in prostate cancer, because it is highly and specifically expressed on the surface of prostate tumor cells at all tumor stages. In recent years, there has been increasing focus on PSMA as a target for both imaging and

therapy. Small-molecule high-affinity PSMA antagonists have been developed and are labeled with ^{68}Ga, ^{18}F, ^{11}C, ^{64}Cu, and ^{86}Y [124].

^{68}Ga-PSMA-HBED-CC PSMA (^{68}Ga PSMA) ligand is a related small-molecule PSMA antagonist that has up to now been the most clinically used PSMA PET radiotracer in prostate cancer patients. Afshar-Oromeih et al. [125] performed a retrospective analysis in 319 prostate cancer patients who underwent ^{68}Ga PSMA ligand PET/CT. The study included primary, biochemical recurrence, and metastatic cancers. ^{68}Ga PSMA can detect prostate cancer in a high percentage of patients with suspected cancer (82.8%). Tumor-detection was correlated with PSA level and androgen deprivation therapy (ADT). Lesion-based analysis demonstrated a sensitivity of 76.6%, specificity of 100%, negative predictive value of 91.4%, and positive predictive value of 100%. Eiber et al. [63] retrospectively studied 248 patients with biochemical recurrence after radical prostatectomy using ^{68}Ga PSMA and detected a malignant lesion in 89.5%. Detection rates improved with higher PSA levels and higher PSA velocity. The high sensitivity and excellent specificity of ^{68}Ga-PSMA were also reported by other studies [126, 127].

PSMA ligands may also be labeled with ^{18}F for PSMA PET imaging. Pomper et al. [128] reported the study of PET with small-molecule inhibitors of PSMA for the imaging of prostate cancer in animals using *N*-[*N*-[(*S*)-1,3-dicarboxypropyl]carbamoyl]-*S*-[^{11}C]methyl-L-cysteine, a glutamate-urea-cysteine (^{18}F-DCFBC) analog. A human study reported by Cho et al. [129] demonstrated the feasibility and potential of using ^{18}F-DCFBC for the detection of metastatic prostate cancer. In evaluating localized prostate cancer, Rowe et al. [87] studied 13 patients scheduled for prostatectomy who were imaged with ^{18}F-DCFBC PET, with 12 of 13 patients also undergoing prostate MR imaging. ^{18}F-DCFBC PET was able to detect more clinically significant high-grade and larger-volume tumors (Gleason score 8 and 9) with higher specificity than MR imaging.

PET/ultrasound fusion targeted biopsy

Fei and colleagues developed an approach for PET molecular image-directed, 3D ultrasound-guided biopsy [96, 97]. As shown in Fig. 2, the system uses: (1) passive mechanical components for guiding, tracking, and stabilizing the position of a commercially available transrectal ultrasound probe; (2) software components for acquiring and reconstructing a series of real-time 2D TRUS image slices into a 3D image volume of the prostate; and (3) software that segments the prostate gland in the 3D TRUS image volume and then displays a 3D model to guide a biopsy needle to the suspicious target lesions in three dimensions. The system allows real-time tracking and recording of the 3D position of the biopsy sites as a physician manipulates the ultrasound transducer. An offline workstation system is used to register and fuse PET/CT and ultrasound images.

Clinical workflow

The clinical protocol for PET/CT directed, 3D ultrasound-guided biopsy of the prostate is shown in Fig. 3. Before undergoing the targeted biopsy, the patient undergoes a PET/CT scan as part of his examination. The anatomic CT images are registered with the PET images for improved localization of the prostate and suspicious lesions. (1) The patient undergoes a

3D ultrasound scan ("pre-biopsy" image) before the actual biopsy appointment. This planning scan may be performed at any time before the biopsy and even on the same day of the PET/CT scan. (2) The PET/CT and pre-biopsy ultrasound images are registered offline before biopsy. (3) Immediately before biopsy, another 3D ultrasound image volume is acquired before the biopsy planning. These "intra-biopsy" ultrasound images are registered with the pre-biopsy ultrasound image volume. As the pre-biopsy ultrasound image volume has been registered with the PET/CT volumes; in turn, the PET/CT image is also registered with the intra-biopsy ultrasound image volume for tumor targeting. Three-dimensional visualization tools are then used to guide the biopsy needle to a suspicious lesion. (4) The position of the needle tip is recorded on real-time ultrasound images during the biopsy procedure. The location information of biopsy cores is saved and can be restored in a re-biopsy procedure if necessary. This allows the physician to re-biopsy the same area and monitor potential progression or treatment effect of a lesion. The location information of the biopsy cores can also be used to guide another additional biopsy to different locations if the original biopsy was negative. Figure 4 shows the clinical setup of the PET molecular image-directed, 3D ultrasound-guided biopsy.

Prostate segmentation and deformable registration

To use the 3D model of the prostate to guide a biopsy needle to the targeted, two key techniques are required for fusion targeted biopsy. The first technique is automatic segmentation of the prostate on the 3D TRUS image volume. The second technique is deformable registration between the 3D TRUS image volume and molecular images (PET/CT or mp-MRI).

Image segmentation

Segmentation of the prostate in a 3D ultrasound volume is a key technique of the 3D ultrasound image-guided biopsy. However, segmentation of the prostate in ultrasound images can be challenging because of shadowing from the bladder and because of low contrast between the prostate and adjacent tissue. Fei et al. developed an automatic method to segment the prostate in 3D TRUS images [97, 98]. This method utilizes the wavelet-based texture extraction technique followed by support vector machines (SVMs) to adaptively collect texture priors of prostates and non-prostate tissues and classify tissues in different sub-regions around the prostate boundary by statistically analyzing their textures using wavelet features [98]. Figure 5 shows the 3D prostate after image segmentation.

Extensive work has been carried out to develop methods to successfully segment the prostate from MR images [99–106]. It can also be challenging to accurately segment the prostate in T2W-MRI. Contour- and shape-based methods [107–111] exploit edge information and shape features to segment the prostate. One group of methods involves edge-based segmentation. The edge detection operators are used to produce edges on MR images. The candidate edges are picked up and then connected to obtain the prostate boundary. Zwiggelaar et al. [107] developed a semi-automatic method to segment the prostate in MRI data. The edge detection and non-maximum suppression are used to track the boundary of the prostate. The second group of methods involves deformable model based segmentation.

Kass et al. [112] proposed an active contour model and used image gradient to evolve a curve for segmentation. Chan and Vese [113] proposed a level set algorithm of the piecewise constant variant of the Mumford-Shah model [114] for segmentation.

Other segmentation methods have also proposed for prostate. Ghose et al. [115] reviewed segmentation methods for the prostate in TRUS, MR and CT images. Klein et al. [116] proposed an atlas-based method for segmenting the prostate in 3D MR images. Egger [117] studied a graph-based approach to automatically segment prostate based on a spherical template. Mahapatra and Buhmann [100] suggest a fully automatic method for prostate segmentation using random forests classifiers and graph cuts. Finally, Tian et al. advocate a supervoxel-based segmentation method for the prostate [118, 119].

Image registration

Image registration is a process of aligning two or more images, which aims to find the optimal transformation that best aligns the structures of interest in the input images. For molecular image directed, 3D ultrasound-guided biopsy, registration incorporates the data obtained from high sensitivity molecular imaging with real-time ultrasound for targeted biopsy of suspicious lesions.

To incorporate lesion information from PET/CT into the 3D ultrasound-guided biopsy, image registration plays a key role in combining the two imaging multimodalities. However, deformable registration of ultrasound and PET/CT images is difficult for the following reasons: (1) neither PET nor ultrasound contains enough structural information about the prostate for direct intensity-based image registration; (2) ultrasound provides only a small field of view that covers just the prostate and surrounding tissue which is only a small portion of a PET image that includes the entire pelvic region; and (3) the significant prostate deformation caused by the transrectal probe disqualifies registration algorithms that assume small deformation. Fei et al. [120, 121] used CT images as the bridge to register PET with TRUS, because both PET and CT images are acquired from a combined PET/CT system. The registration method is a hybrid approach that simultaneously optimizes the similarities from point-based registration and volume matching methods. The 3D registration is obtained by minimizing the distances of corresponding points at the surface and within the prostate and by maximizing the overlap ratio of the bladder neck on both images. The hybrid approach not only capture deformation at the prostate surface and internal landmarks but also the deformation of the entire organ.

For MRI/TRUS fusion targeted biopsy, image registration is needed to integrate the features from different images of mp-MRI, such as DCE-MRI and T2W MRI. The registration of images requires the selection of the feature space, a similarity measure, a transformation type, and a search strategy [122]. The DICOM header of MR images can provide coordination and orientation information that are useful for registering T2W, ADC, and K^{trans} maps. T2W-MRI is considered as the reference. Other modalities can be registered to T2W-MRI by aligning the coordinates of their origins, which are obtained from the DICOM header. If necessary, resolution adjustment is also performed after the alignment.

Conclusion and future directions

Molecular image-directed, 3D ultrasound-guided biopsy represents a new trend for the diagnosis of prostate cancer and for monitoring of prostate cancer for patients on active surveillance. MRI/TRUS fusion targeted biopsy is a new standard of care, approved by U.S. Food and Drug Administration. PET/ultrasound fusion targeted biopsy is a new direction that can have an immediate impact on future patient care. (1) For patients who select active surveillance and whose biopsy result shows a low-grade, non-clinically significant tumor, an accurate biopsy can help to reduce their anxiety that often increases due to possible sampling error and the uncertainty associated with the current biopsy technique. As a false negative result may delay treatment, an accurate biopsy is extremely important for those active surveillance patients and for those patients undergone focal therapy for a small volume prostate cancer. (2) For patients diagnosed on biopsy as having premalignant lesions, i.e, high-grade prostatic intraepithelial neoplasia, and, in particular, atypical small acinar proliferation (ASAP), the biopsy result is clinically significant as there is a 40–80% chance of finding cancer on repeat biopsy if there is ASAP [9]. As there might be coexisting cancer, especially with ASAP, where the pathologist finds only a small amount of histological “atypia” that is suboptimal for a definitive diagnosis of cancer; such patients require a repeat biopsy soon after the first one. For ASAP patients, it is vital to re-biopsy the same area. Unfortunately, 2D ultrasound provides imprecise location of the abnormal findings, and it is not possible to be certain that the same area has been sampled by the repeat biopsy. 3D ultrasound image-guided biopsy is able to record the 3D location of the biopsy sites for follow-up examinations and thus will change the management of these ASAP patients. (3) If the targeted biopsy improves cancer detection rate, many patients would not need repeated biopsies, and the total number of prostate biopsies could be reduced. Furthermore, it will also reduce the potential morbidities of life-threatening sepsis and transrectal bleeding, both of which are associated with biopsy procedures. The use of PET/ultrasound fusion targeted biopsies within the diagnostic pathway may result in an enhanced detection of clinically significant disease, fewer men diagnosed with clinically insignificant disease, fewer men biopsied overall, and fewer needle deployments; thus it could transform prostate cancer management and change clinical practice from “blind” to “targeted” biopsy. (4) With the advancement of combined PET/MRI, MRI can also be directly used to guide biopsies; however, this approach can have high cost and long procedure time [7, 46–49]. (5) There are still technical challenges for molecular image-directed, 3D ultrasound-guided biopsy, which include the development of accurate, automatic, and fast segmentation methods and reliable, deformable registration algorithms. (6) The collaboration between academic medical center and industry can play an essential role in bringing new fusion targeted biopsy technology to benefit patients and change the routine clinical practice.

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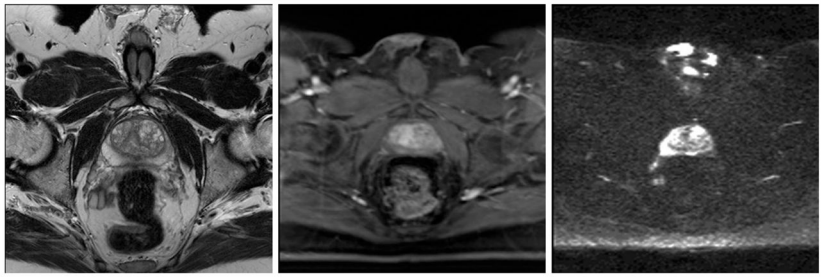

Fig. 1.

Multiparametric MRI of the prostate: T2-weighted MRI (*left*), DCE-MRI (*middle*), and diffusion-weighted MRI (*right*) of the same patient

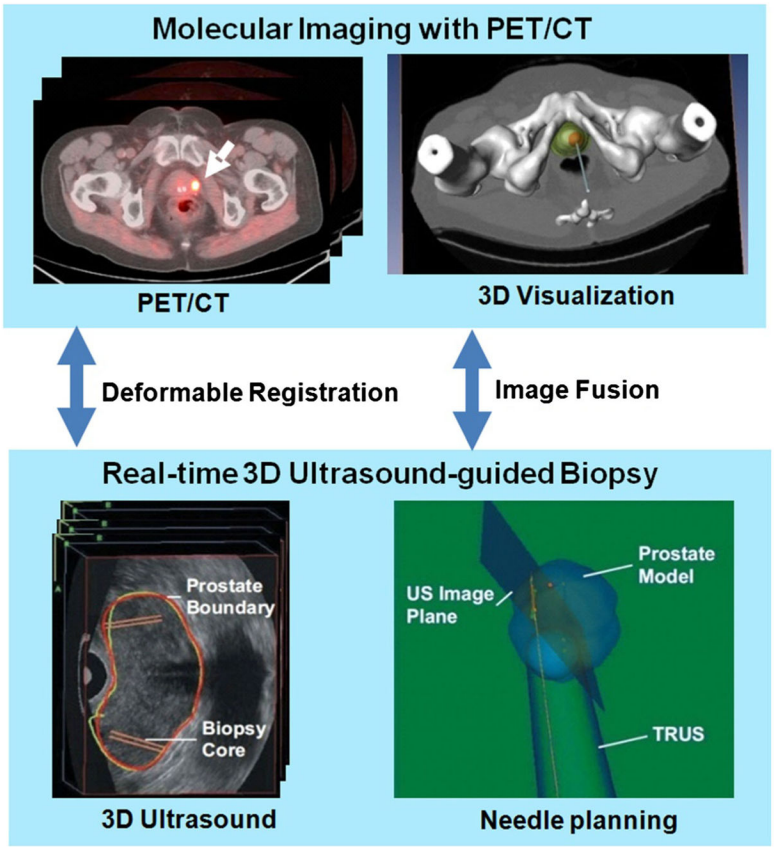

Fig. 2.

PET/ultrasound fusion targeted biopsy. *Top* the PET/CT images with fluciclovine were acquired from a human subject. PET/CT images show a focal lesion within the prostate (*white arrow*). The 3D visualization of the pelvis and the prostate were used to aid the planning of the biopsy to a suspicious tumor target. *Bottom* during biopsy, a mechanically assisted navigation device, was used to acquire 3D TRUS images from patients. The prostate boundaries on TRUS images were segmented and were used to generate a 3D model of the prostate. The 3D prostate model and real-time TRUS images are used to guide the biopsy in patients [96]

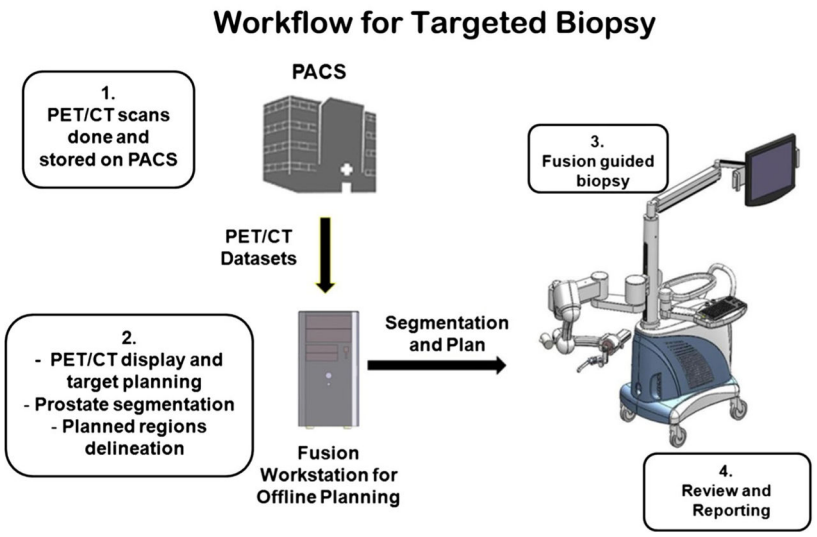

Fig. 3.
Clinical workflow for the PET/ultrasound fusion targeted biopsy

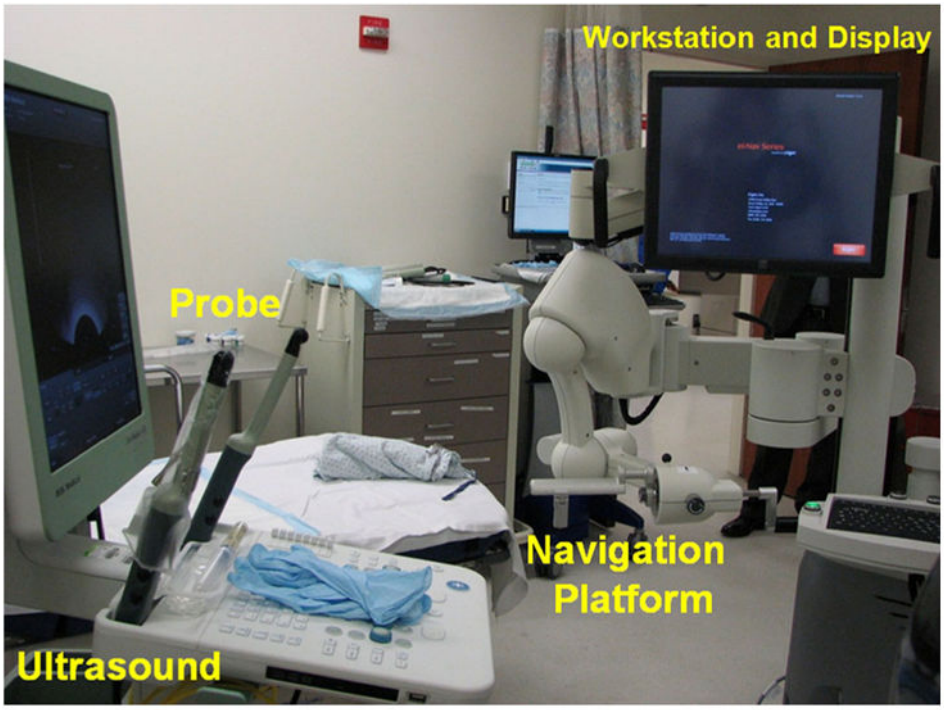

Fig. 4.

Setup for the molecular image-directed, 3D ultrasound-guided biopsy system that includes a commercial ultrasound scanner and an end firing probe from B&K Medical, the Artemis system, and a workstation for image fusion

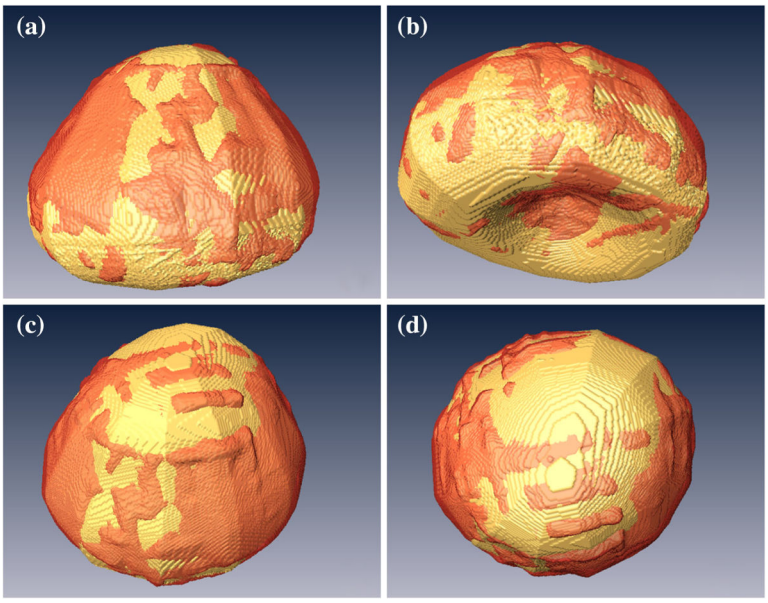

Fig. 5.

3D visualization of the automatically segmented prostate (*red*) as compared with the manual segmentation gold standard (*gold color*) in *four different views* (**a**–**d**) of the same human prostate Reprint from Akbari et al. [98]

Table 1

Selected studies on MR/TURS fusion targeted biopsy by the NCI and UCLA groups

Study	Patient demographics			MR				Fusion platform	Underwent 12-core systematic biopsy	Target biopsy		
	Sample size (*n*)	Mean/Median age (year)	Median PSA (ng/ml)	Median prostate volume (cc)	MR scanner	ER coil	Average lesions per patient			Cores per patient	Cores per lesion	Overall cancer detection
Pinto et al. 2011 [38]	101	63 (41–82)	5.8 (0.2–103)	–	3.0T, Achieva, Philips	Yes	2.6 (1–7)	UroNav	Yes	5.8	2.2 (1–8)	27.9%, 66.7%, 89.5%^
Vourganti et al. 2012 [40]	195	62 (37–80)	9.13 (0.3–103)	56 (16–187)	3.0T, Achieva, Philips	Yes	2 (1–7)	UroNav	Yes	–	–	15.22%, 38.14%, 67.14%^
Siddiqui et al. 2015 [52]	1003	62	6.7 (4.4–10.7)	49 (36–71)	3.0T, Achieva, Philips	Yes	2.7	UroNav	Yes	5.3	–	46.0% (461/1003)
Sonn et al. 2013 [54]	171	65	4.9	48	3.0T, Somatom, Siemens	No	1.6 (0–4)	Artemis	Yes	13.4	2.2 (1–6)	48%, 56%, 94% *
Sonn et al. 2014 [56]	105	65 (59–70)	7.5 (5.0–11.2)	58 (39–82)	3.0T, Somatom, Siemens	No	1.3 (1–3)	Artemis	Yes	15.9	4.2 (1–9)	4%, 21%, 75% *
Hu et al. 2014 [57]	113	63 (58–68)	4.2 (2.6–6.3)	46.8 (36.1–64.5)	3.0T, Somatom, Siemens	No	–	Artemis	Yes	4	–	77%
Sonn et al. 2014 [59]	53	64 (59–69)	4.3 (2.2–6.4)	48 (36–60)	3.0T, Somatom, Siemens	No	–	Artemis	Yes	–	–	39%
Muller et al. 2015 [130]	10	63 (56–68)	–	–	3.0T, Achieva, Philips	Yes	1.6	UroNav	No	–	–	80% (8/10)
Sankineni et al. 2015 [131]	33	63 (52–76)	6.1 (1.22–65.2)	53 (12–125)	3.0T, Achieva, Philips	Yes	–	UroNav	Yes	–	–	72.7% (24/33)
Walton et al. 2013 [132]	649	62	6.65	58.7	3.0T, Achieva, Philips	Yes	–	UroNav	Yes	–	–	55% (357/649)
Le et al. 2014 [133]	54	62	6.2 (5.0–10.9)	–	3.0T, Somatom, Siemens	No	1.9	Artemis	Yes	5.9 (4–8)	–	5.5%, 69%, 75% *
Filson et al. 2016 [134]	1042	65.7 (59.3–70.2) +	7.6 (5.0–11.5) +	57.7 (39.8–83.5) +–	3.0T, Somatom, Siemens	No	1.5	Artemis	Yes	–	–	16%, 33%, 69% *

ER endorectal, – Not available

* For regions of interest (ROIs) on MRI with Grade 3, 4, and 5, respectively

^ For patients with low, moderate, and high suspicion, respectively

\+ The group of prior negative biopsy (N=324)