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New Horizons in Prostate Cancer Imaging

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Abstract

Prostate cancer is the most common non-cutaneous malignancy among American men. Imaging has recently become more important in detection of prostate cancer since screening techniques such as digital rectal examination, prostate specific and transrectal ultrasound guided biopsy have considerable limitations in diagnosis and localization of prostate cancer. In this manuscript, we reviewed conventional, functional and targeted imaging modalities used in diagnosis and local staging of prostate cancer with exquisite images.

Prostate cancer is the most common malignancy among American men and the second leading cause of cancer related deaths [1]. The frequency of prostate cancer increases with age and with the widespread use of screening tests (e.g. serum prostate specific antigen [PSA] and digital rectal examination (DRE)); on the other hand the mortality rate of prostate cancer has improved over the last 4 years. Prostate cancer remains a major health care problem and a significant cause of morbidity and mortality.

The screening tools for prostate cancer have limitations. Although digital rectal examination (DRE) is a mainstay of diagnosis it has significant limitations. For instance, it is nearly impossible to detect sub-centimeter lesions with DRE. However, on occasion it is only DRE that is capable of detecting non-PSA-producing tumors, many of which are biologically aggressive.

The other major screening tool is serum prostate specific antigen (PSA). PSA was first introduced by Wang et al. in the late '70s [2]. It is a serine protease which is abundant in seminal fluid, but is normally found in low concentrations in serum. Two forms of PSA exist in the serum: a protein-bound form and a free or unbound form. "Normal" PSA, i.e. PSA produced by normal tissue, is less likely to be bound to protein whereas the PSA produced by cancers is "sticky" and therefore binds to proteins in a higher percentage. Thus, when the free PSA is >30% the likelihood of cancer is low, whereas when it is <25% the likelihood of cancer increases. The "normal" value for total PSA is controversial but is generally quoted as <4ng/ml. However, lower thresholds may be used especially if the PSA is rising rapidly. For instance, a high "PSA velocity" (>0.75ng/ml/year) is not only suggestive of prostate cancer but also may be related to tumor aggressiveness. As PSA can also be elevated in prostatitis, benign hyperplasia and trauma the combined use of total PSA and PSA velocity may be helpful for differentiation of prostate cancer from other benign etiologies [3,4]. Patients with abnormal

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DRE findings and elevated PSA values should be further evaluated for presence of prostate cancer via TRUS guided biopsy.

Transrectal ultrasonography (TRUS)

TRUS is the most commonly used modality for imaging the prostate gland. TRUS enables the accurate determination of prostate size which is useful in determining the “PSA density” (PSA/prostate volume) but its ability to delineate cancer foci is limited. Using high resolution probes, TRUS can demonstrate the zonal anatomy of prostate gland (figure 1).

When a cancer is visualized by ultrasound it is usually hypoechoic relative to normal tissue, but small cancer foci are often not demonstrated at all; moreover the majority of hypoechoic foci detected by TRUS are not malignant, therefore both its sensitivity and specificity are low [5] (figure 2). TRUS is also rarely useful in demonstrating extracapsular extension (ECE) of prostatic cancer and seminal vesicle invasion (SVI) except when gross extension is present and this is usually palpable. ECE is usually seen as capsular bulging and/or a contour irregularity with obliteration of the rectoprostatic angle; SVI can be seen as a hypoechoic solid lesion within the normally cystic seminal vesicles [6]. However, TRUS is mainly used to guide prostate biopsies and not stage prostate cancer. Indications for TRUS guided prostate biopsy include elevated PSA ($>4\text{ng/ml}$) and/or a PSA velocity of greater than 0.75ng/ml/year and/or abnormal DRE findings. The sensitivity of TRUS guided sextant biopsy for cancer detection varies around 60% and depends on the demographics of the population being studied. The recent trend in TRUS guided biopsy is to obtain at least 10-12 cores; Stamatiou et al demonstrated the efficacy of this approach for individuals with high PSA but negative DRE [7]. However, it is unclear whether this approach simply detects more clinically occult tumors or results in a true benefit. The addition of Color and/or Power Doppler can increase the rate of prostate cancer detection by detecting regions of hypervascularity [8]. Contrast enhanced TRUS with microbubbles, provides higher sensitivity for detection of cancer foci. Besides contributing to the diagnostic imaging workup, contrast enhanced TRUS can detect prostate cancer in patients with previous negative biopsies but persistently rising PSA values [9,10].

Computed Tomography (CT)

The contrast resolution of CT is insufficient to distinguish the prostatic anatomy from other adjoining structures (e.g. muscles, bladder wall etc.) and it is usually impossible to detect cancers within the prostate gland. The ability of CT to depict extracapsular extension (ECE) is limited except in cases of gross extension. Therefore, CT has a very limited role in tumor detection and staging of prostate cancer [11-13] (figure 3). The main role of CT is in nodal staging and in delineating bone metastases. Because prostate cancer is slow growing, nodal enlargement is not a primary feature. Since CT relies on size measurements to determine nodal involvement, CT is limited in most patients presenting with cancer in the PSA era because the nodes are usually not enlarged. CT is more useful in high risk individuals with PSA $> 20\text{ng/ml}$, Gleason score of >7 and tumor stage of T3 or higher, where the likelihood of a positive node is more likely (figure 4). Whole body CT also allows detection of distant organ and/or bone involvement, however bone scans and especially MR imaging are more sensitive for bony disease [13]. Thus, CT plays a minor role in the overall assessment of prostate cancer.

Magnetic Resonance (MR) Imaging

MR imaging allows unparalleled anatomic assessment of the prostate with better soft tissue resolution than any other imaging modality. Such detailed anatomic information can be used not only for the detection but also for staging. The highest resolution MR image requires the use of an endorectal coil and phased-array body coil on a magnet with a field strength of at least 1.5T. Although body coil images can be entirely satisfactory for some indications, images

obtained with the endorectal coil/phased array surface coil combinations produce much higher signal to noise ratios (SNR) which can be used to improve the image resolution, acquisition speed or both.

Conventional MR imaging of the prostate gland includes T1 and T2 weighted (W) sequences. T1W images are obtained in the axial plane and demonstrate homogenous low signal intensity and it is not possible to differentiate the zonal anatomy. T1W images can show the presence of hemorrhage secondary to a recent biopsy that is almost always hyperintense compared with normal parenchyma. The T2W images are obtained in all three planes (axial, coronal and sagittal), and are used for identifying low signal areas in the peripheral zone and ECE. On MRI the peripheral zone (PZ) appears high in signal on T2W images whereas the central gland (including the transitional and central-periurethral zones) has lower signal intensity. The central gland (CG), which includes the transitional zone (TZ) and central zone (CZ) is separated from the PZ by a pseudocapsule which is different from the true capsule, a hypointense rim surrounding the PZ. The neurovascular bundles are located at approximately 5 and 7 o'clock on the axial image and demonstrate both high and low signal intensity foci lying posterolateral to the true capsule. The seminal vesicles appear as hyperintense on T2W images (figure 5) whereas the paired vas deferens, which lie medial to the seminal vesicles are low in signal intensity.

On T2W images, PZ cancers are usually round or ill-defined, low signal intensity foci (figure 6). Various conditions can mimic cancer such as prostatitis, hemorrhage, atrophy, benign hyperplasia and post-treatment changes. Cancers in the central gland are more difficult to detect since the signal characteristics of the central gland usually overlap with those of the tumor (figure 7). Detecting prostate cancers in hyperplastic TZs is especially problematic due to the heterogeneity of the background. Akin et al. in a retrospective study of 148 patients defined characteristics of a TZ tumor which included: a homogenous low signal intensity lesion with irregular margins without a capsule, and invasion of the pseudocapsule, with lenticular, urethral and anterior fibromuscular invasion [14].

ECE can be detected on T2W images based on visualizing direct extension of the tumor into the periprostatic fat [15] (figure 8). The secondary findings of ECE include asymmetry of the neurovascular bundle, tumor envelopment of the neurovascular bundle, contour angulation, irregular gland margin, capsular obscuration or retraction, and obliteration of the rectoprostatic angle [16] (figure 9). Seminal vesicle invasion (SVI) can be directly visualized as extension of tumor from the base of prostate, and the presence of focal low signal intensity within the seminal vesicles [17]. For optimum detection of ECE and SVI, high resolution T2W images should be evaluated in all three planes since it is impossible to predict the best plane of section. (figure 10).

Biopsy related hemorrhage causes a well known artifact that limits the detection of prostate cancer, since hemorrhage can mimic a cancer in the PZ on T2W scans. However, post biopsy hemorrhage usually demonstrates high signal intensity on T1W images whereas cancers do not (figure 11). Post-biopsy hemorrhage not only interferes with accurate evaluation of T2W images but also will confound dynamic contrast enhanced MR and MR spectroscopy. The time interval between the biopsy procedure and MR imaging generally should be at least 8 weeks to ensure that the T2W imaging is not confounded by hemorrhage [18].

Dynamic Contrast Enhanced (DCE) MR Imaging

DCE MR imaging evaluates the vascularity in tumors by providing quantitative kinetic parameters reflecting wash-in and wash-out. Vascularity of a neoplastic lesion depends on its blood supply and its capillary permeability. Fast MR scanning sequences combined with the rapid administration of a low molecular weight contrast agent may enable detection of leaky

vessels within tumors. Recently, Ocak et al. reported the utility of DCE MR imaging in detecting prostate cancer using 3D fast spin echo sequences and a two compartment pharmacokinetic model and demonstrated that DCE-MRI increases specificity of prostate MRI significantly over T2W scans alone [19]. Tumors showed early enhancement with DCE-MRI. Early washout is another distinctive feature of malignancy. The enhancement curves can be mathematically fit to two compartment pharmacokinetic models such as the Toft's model (figure 12) producing wash in and wash out parameters. Higher grade tumors tend to have higher wash in and washout parameters. Abnormal enhancement patterns are seen in both tumor foci and BPH nodules making assessment of the central gland difficult [20]. However, it is important to note that smaller and low grade tumors may not demonstrate abnormal enhancement on DCE-MRI.

MR Spectroscopy (MRS)

MRS provides information about the cellular metabolites within the prostate gland by displaying the relative concentrations of key chemical constituents such as citrate, choline and creatinine. The normal prostate gland contains low levels of choline and high levels of citrate, whereas prostate cancer lesions demonstrate high levels of choline and decreased levels of citrate. The high choline levels in cancer are related to increased cell turnover. There is an increased amount of soluble free choline compounds [21] due to overexpression of choline kinase in prostate cancer tissue, which is also observed in colon and lung cancers [22]. Normal secretory epithelial cells of prostate gland produce high levels of citrate and normal prostate glandular cells possess excess zinc (the highest levels in the body are found in the prostate). Zinc inhibits the citrate oxidizing enzyme “aconitase” and blocks the Krebs cycle leading to accumulations of citrate. However, in prostate cancer cells, levels of zinc are lower, leading to elevated aconitase activity and oxidation of citrate leading to diminished amounts in cancer cells [23,24] (figure 13).

The criteria for prostate cancer on MRS rely on increased choline-citrate ratios (figure 14). The majority of the prostate MRS imaging data in the current literature is derived from 1.5T magnet systems and since the choline peak can not be discriminated from the creatine peak, the ratio measured is really that of choline plus creatine to citrate (*cho+cre/cit*). Kurhanewicz et al [25] have classified voxels as normal, suspicious and very suspicious for cancer based on the *cho+cre/cit* ratios. Suspicious voxels have a (*cho+cre/cit*) ratios within 2 standard deviations higher than the normal average ratio within the PZ, whereas very suspicious voxels have a ratio that is greater than 3 standard deviations above the normal average. Integration of MRS into routine prostate MR imaging practice has improved tumor detection rates in several studies [26-28] and might be useful in identifying transitional zone tumors [29]. Moreover, MRS has been used to help in the estimation of tumor volume, extracapsular extension and post-radiotherapy recurrence [15, 30-33].

Most MRS studies have been performed on 1.5T magnets. Recently, 3T and higher field strength magnets have been employed to obtain prostate MRS. Increased field strength leads to increased signal to noise ratios (SNR), smaller voxel size, improved temporal resolution, and more accurate separation of metabolite peaks. For instance, MRS performed at 3T enables distinction of the choline peak from the creatine peak, improving specificity [34]. Besides choline, citrate and creatine analysis, newer image acquisition and analysis software may enable evaluation of other metabolites such as the polyamine peaks; Shukla-Dave et al reported the feasibility of evaluating polyamines by MRS and concluded that the polyamine peaks may be lower than the choline peak in tumors [35].

Diffusion Weighted Imaging (DW-MRI)

DW-MRI evaluates the Brownian motion of free water in tissue. Tissue diffusion is found to be restricted with increased cellularity since the water path is interrupted by cell membranes. Prostate cancer lesions often include tightly packed glandular elements with increased cellularity and diminished extracellular spaces which can be detected with DW-MRI as regions of restricted diffusion. Prostate cancer lesions appear as high signal intensity foci on raw DW-MRI but are low in signal on ADC maps [36] (figure 15). Recently, DW-MRI was shown to be helpful in detecting small prostate cancers [37-39]. DW-MRI is characteristically a low SNR imaging sequence, but with the emergence of high field strength magnets and the widespread use of endorectal coils, high resolution DW-MRI imaging can be performed. Additionally, usage of higher b values (0 to 1000 s/mm²) improves its performance for lesion detection [40,41].

Positron Emission Tomography (PET)

PET is emerging as an important research tool in prostate cancer. In PET, a trace amount of a radioactive compound is administered and the resultant images are 3 dimensional spatial reconstructions of the tracer at the time of imaging. The intensity of the imaging signal is proportional to the amount of tracer and, therefore is potentially quantitative. While the routine clinical spatial resolution is limited (~ 4-6 mm), the ability to image physiological processes, such as the rate of glucose metabolism, provides information not available from conventional imaging techniques.

¹⁸F-Fluorodeoxyglucose

The principle of ¹⁸F-fluoro-2-deoxy-2-D-glucose (¹⁸F-FDG) imaging is based on Warburg's observation that the increased metabolic demands of rapidly dividing tumor cells require adenosine triphosphate (ATP) generated by glycolysis [42]. FDG is actively transported into cells and converted into FDG-6-phosphate by hexokinase. Since FDG-6-phosphate is not a substrate for the enzyme responsible for the next step in glycolysis, it is then trapped and accumulates in the cell in proportion to its metabolic activity [43].

¹⁸F-FDG has been shown to be helpful in staging, and monitoring response to treatment in a variety of tumors. However, certain slow-growing tumors such as broncho-alveolar carcinomas, indolent lymphomas, and well-differentiated hepatocellular carcinomas are less ¹⁸F-FDG avid. In fact, several studies have confirmed that ¹⁸F-FDG is not effective in the diagnosis of localized prostate cancer and only becomes positive in patients with more advanced, androgen independent tumors (figures 16 and 17) [44, 45]. To complicate matters even further, several studies have demonstrated significant overlap between ¹⁸F-FDG uptake in prostate tumors and benign prostatic hyperplasia [46]. An additional confounding problem is that ¹⁸F-FDG is excreted through the kidneys and intense activity is usually present in the urinary bladder obscuring the prostate and interfering with identification of pelvic lymph node metastases [47]. Therefore, ¹⁸F-FDG, is not the ideal PET tracer for the initial staging of prostate cancer.

Even in cases of recurrent disease ¹⁸F-FDG has been disappointing. In one study performed at the Memorial Sloan-Kettering Cancer Center, ¹⁸F-FDG was false-negative in 60 out of 91 patients with recurrent disease. The probability of disease detection correlated with PSA values and in particular with the velocity of PSA increase (PSA of 2.4 ng/ml, PSA velocity of 1.3 ng/ml/year) [48] but not with PET results.

In general, ¹⁸F-FDG uptake in metastatic prostate cancer seems to reflect the biology of the tumor. Morris *et al* examined patients with progressive metastatic disease and concluded that ¹⁸F-

FDG has a stronger role in differentiating active osseous disease from scintigraphic quiescent lesions [49]. Even so, as ^{18}F -FDG targets only a specific property of cancer metabolism (glucose utilization) there is a clear need for other novel PET radiotracers.

Novel positron-emitter radiotracers

^{11}C -Acetate

Acetate (AC) is a naturally occurring compound that is converted to acetyl-CoA, a substrate for the TCA cycle, and is incorporated into cholesterol and fatty acids [50]. Even though the exact mechanism of acetate accumulation in tumors is unknown, it is hypothesized that AC becomes incorporated in the membrane lipids of tumor cells [50]. AC is metabolized in various organs and is excreted via the pancreas, enabling imaging of the pelvis without confounding bladder activity. For this reason ^{11}C -acetate (^{11}C AC) PET may be able to detect and potentially monitor treatment in patients with prostate cancer.

Oyama *et al* investigated prostate cancer with ^{11}C AC [51] in 22 patients with primary prostate cancer. Eighteen of the 22 also underwent ^{18}F -FDG PET scans. Of the 22 patients, only 5 underwent radical prostatectomy. In the remainder 17 patients, histology was obtained by TRUS sextant biopsy. ^{11}C AC uptake in primary prostate tumors was positive in all patients, whereas ^{18}F -FDG was positive in only 15 out of 18 patients. Furthermore, ^{11}C AC was superior in the evaluation of pelvic lymph nodes and was able to identify metastases in 5 patients versus 2 with ^{18}F -FDG. In 7 patients with bone metastases detected by $^{99\text{m}}\text{Tc}$ -HDP, ^{11}C AC was positive in 6, whereas ^{18}F -FDG was only positive in only 4 patients. Thus, ^{11}C AC shows promise in comparison to ^{18}F -FDG.

Kotzerke *et al* [52] studied the potential utility of ^{11}C AC in the detection of local recurrent prostate cancer in 31 patients. Results were compared with TRUS biopsy and clinical follow-up. Non-attenuation-corrected PET images were obtained 5 minutes after radiotracer administration. ^{11}C AC positively identified local recurrence in 15 of 18 patients. Of the 3 patients with false-negative results, tumor volumes were very small in two patients (0.1 and 0.3 ml). However, in 1 patient the lesion was not detected despite a reasonable tumor volume (~1.5 ml). 13 patients without ^{11}C AC uptake were proved to be true-negatives by TRUS biopsy and follow-up.

Studies by Fricke *et al* compared ^{11}C AC and ^{18}F -FDG in patients with rising PSA after radical prostatectomy and radiation therapy [53]. ^{11}C AC detected relapse in 20 out of 24 patients whereas ^{18}F -FDG was positive in 10 out of 15. Moreover, ^{11}C AC lesion demonstrated significantly higher uptake than ^{18}F -FDG (medium SUV ^{11}C AC lesions = 3.2, medium SUV ^{18}F -FDG lesions = 1.4). However, the current literature is lacking large, controlled studies. As described in an excellent review by Morris and Scher, the current data is simply too small to draw anything but the most preliminary conclusions [54]. Prospective well controlled trials are necessary in order to properly evaluate the role of ^{11}C AC PET/CT in this setting. Moreover, the value of combining ^{11}C AC with 3T MRI needs to be further explored [55]. While overlap of ^{11}C AC uptake between malignant and hyperplastic prostate tissue has been reported [56], correlation with MRI and MRS should increase the specificity of this test in the evaluation of organ confined disease. Since prostate cancer is often multi-focal, it is hoped that in the near future novel tracers such ^{11}C AC can be used in conjunction to 3T MRI to differentiate between low and high risk tumor foci and guide organ sparing therapy.

The short half-life of ^{11}C (~20 minutes) requires that scans be performed in close proximity to a cyclotron, which will limit widespread clinical utility. Accordingly, there is significant interest in the development of acetate analogs labeled with ^{18}F (half-life ~ 110 min) such as 2- ^{18}F -fluoroacetate [57]. Conversely, the short half-life of ^{11}C AC provides a unique

opportunity for multi-tracer evaluations with limited radiation exposure to research participants.

^{11}C -Choline and ^{18}F -Fluorocholine

^{11}C -choline is used clinically in Europe but not in the United States. As mentioned in the discussion of MR Spectroscopy, Choline is an important component of the phospholipids in the cell membranes and elevated levels of choline and choline kinase (CK) have been detected in cancer cells. [58]. Several choline analogs have been labeled with ^{11}C or ^{18}F for PET imaging [59,60]. Similar to acetate, ^{11}C -choline has limited urinary excretion and thus, is well suited for prostate imaging.

^{11}C -choline was first introduced as a potential radiotracer for imaging prostate cancer by Hara *et al* [61]. In a subsequent study, Farsad and colleagues retrospectively reviewed 36 patients with primary prostate cancer and 5 control subjects with transitional cell carcinoma of the bladder [62]. ^{11}C -choline PET/CT was performed before prostate biopsy and all patients underwent radical prostatectomy within 1 month of ^{11}C -choline PET/CT scans. The mean pre-operative PSA in the prostate cancer group was 12.3 ng/mL (range 2-70 ng/mL). Pathologic correlation was performed with histological step-section analysis of the prostate on a sextant basis. ^{11}C -choline demonstrated focal uptake in 108 sextants (94 of which involved tumor), and 108 sextants showed no abnormal ^{11}C -choline uptake (49 of which were false negative). The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of PET/CT with ^{11}C -choline were 66%, 81%, 71%, 87%, and 55%, respectively. Due to high rates of false-negative and false-positive results, the authors concluded that imaging in this setting with ^{11}C -choline is problematic. Similar to ^{11}C AC, high uptake of ^{11}C -choline is also detected in areas of benign prostatic hyperplasia [63]. Testa *et al* compared ^{11}C -choline PET/CT to endorectal coil 1.5 T MRI and MRS in patients with primary prostate cancer.[64]. ^{11}C -choline demonstrated lower sensitivity relative to MRS imaging alone or to the combined MRI/MRS approach. A correlation between the additive value of combining all diagnostic methods (i.e. MRI/MRS + ^{11}C -choline) to each modality separately was not performed.

In a study by Schiaviana *et al* [65] 57 patients with prostate cancer underwent ^{11}C -choline PET/CT for pre-operative lymph node staging. The population consisted of patients with intermediate and high risk for lymph node metastases. All patients underwent radical prostatectomy and extended lymph node dissection. Results demonstrate that the ^{11}C -choline has a pre-operative sensitivity of 60% and a specificity of 97% and is more accurate than currently used clinical nomograms. As expected, the detection of metastatic deposits is highly influenced by lymph node diameter since ^{11}C -choline is unlikely to identify microscopic disease. For instance, the mean diameter of true-positive lymph nodes was 9.2 mm and false-negatives only 4.2 mm.

The practical aspect of imaging with long-lived radioisotopes has lead to the development of ^{18}F -fluorocholine (^{18}F -FCH). Kwee *et al* evaluated ^{18}F -FCH in 15 patients with organ confined prostate carcinoma [66]. Correlation was performed with step-sectioned radical prostatectomy specimens. Results demonstrated malignant involvement in 61 of 90 prostate sextants. The mean maximum SUV of malignant sextants was significantly higher than on benign sextants (6.0 ± 2.0 vs 3.8 ± 1.4 , respectively; $p < 0.0001$). In all subjects, the highest SUVmax of the prostate localized to a malignant sextant. There was a statistically significant correlation between maximum tumor diameter and SUVmax in malignant sextants indicating the importance of tumor volume in lesion identification.

In another study of 100 patients with PSA relapse by Cimitan and coworkers, ^{18}F -FCH PET/CT led to the identification of prostate cancer recurrence in 53 patients [67]. The investigators found that 89% of the patients with presumably false-negative scans had a serum PSA level <

4 ng/dL. Thus, ^{18}F -FCH may be less sensitive for detecting recurrent prostate cancer if the PSA is low.

It is still too early to determine which of these PET tracers is the best although radiation dosimetry is now known [68,69,70,71]. One of the main disadvantages of choline over acetate is the higher physiologic uptake in the liver parenchyma that can be potentially obscure liver lesions which are uncommon in prostate cancer.

Anti- ^{18}F -FACBC

Anti-1-amino-3- ^{18}F -fluorocyclobutane-1-carboxylic acid (Anti- ^{18}F -FACBC) is a synthetic L-leucine analog developed at Emory University which may have promising prospects in the evaluation of prostate cancer. The mechanism of Anti- ^{18}F -FACBC uptake by cancers cells is not completely understood but appears to be mediated by both the L-type transporter and the energy-dependent A-type transporter. Initial studies demonstrated favorable dosimetry for a 370-MBq injection with high uptake in the pancreas and liver, followed by rapid clearance. Most importantly, bladder excretion was low and initially observed 6 min after injection, well after peak tracer uptake in the body organs. A pilot study of this agent included 15 patients with recently diagnosed or recurrent prostate cancer [72]. After dynamic imaging, correct identification of focal malignancy was achieved in 40 of 48 prostate sextants (figure 18). Pelvic nodal status correlated with anti- ^{18}F -FACBC findings in 7 of 9 patients and was indeterminate in 2 of 9. Even though occasional low-level uptake was seen in benign inguinal lymph nodes, the maximum SUV of malignant adenopathy was significantly higher than of uninvolved nodes. However, the authors acknowledge some limitations of this pilot study such as small sample size and the fact that not all patients underwent prostatectomy with step-sectioned pathology correlation and lymph node dissection or biopsy. Hopefully, larger studies will address some of these issues.

^{18}F -FDHT

Androgen deprivation (AD) is the mainstay treatment of patients with metastatic prostate cancer. AD can be achieved by either removal of the principal source of androgen production (i.e. bilateral orchiectomy) or by administration of drugs such as gonadotropin releasing hormone (GnRH) agonists and nonsteroidal anti-androgens. AD is palliative in nature with limited long-term utility as the disease inevitably progresses to a lethal stage called androgen-independent prostate cancer (AIPC) [73]. Indeed the majority of patients who initially respond to AD will present with disease progression in 12-18 months and succumb to the disease in approximately 2-3 years [74,75,76,77]. Hence, a non-invasive method to evaluate AR expression and functionality may play an important role in monitoring disease progression and treatment response.

16β - ^{18}F -fluoro-5 α -dihydrotestosterone (^{18}F -FDHT), an androgen analog, is a new radiotracer developed at the University of Washington for the purpose of evaluating AR expression *in vivo*. Initial studies performed by Larson *et al* [78] included 7 patients with clinically progressive metastatic prostate cancer who underwent ^{18}F -FDG and ^{18}F -FDHT PET scans in addition to conventional imaging methods. Conventional imaging identified 59 lesions. ^{18}F -FDG was positive in 57 of 59 lesions. ^{18}F -FDHT was positive in 46 of the 59 lesions, with an average lesion maximum SUV of 5.28 and good tumor-to-background ratios (figure 19). Treatment with testosterone resulted in diminished ^{18}F -FDHT uptake at tumor sites. Dehdashti *et al* [79] imaged 20 patients with advanced prostate cancer. All except one had metastatic disease confirmed by biopsy and/or radiological studies.

^{18}F -FDHT PET was positive on a patient-by-patient basis in 12 out of 19 patients and on a lesion-to-lesion basis in 24 out of 28 lesions (excluding two patients with diffuse disease). In

addition, ^{18}F -FDHT PET detected 17 additional metastatic lesions not seen by conventional imaging. All 12 patients with positive ^{18}F -FDHT PET studies underwent repeat PET imaging after anti-androgen drug (flutamide) treatment with significant reduction of radiotracer uptake in all lesions. Radiation dosimetry data for this agent was compiled by Zanzonico *et al* [80] and future studies will perhaps elucidate if ^{18}F -FDHT PET will play a role in selecting patients who will benefit from hormonal treatment and monitor response to therapies targeting ARs.

^{18}F -fluorothymidine

There is currently limited data in regards to the utility of 3'-deoxy-3- ^{18}F -fluorothymidine (^{18}F -FLT) in the management of prostate cancer. ^{18}F -FLT is a structural analog of the DNA constituent, thymidine. ^{18}F -FLT is not incorporated into DNA, but is trapped in the cell due to phosphorylation by thymidine kinase, a part of the proliferation pathway. In this sense it is similar to ^{18}F -FDG: the tracer accumulates in the cell via the same mechanism as the physiological analog, but cannot be further metabolized and is hence "trapped" and continues to accumulate intracellularly. Analogous to ^{18}F -FDG which is a marker of glucose utilization, ^{18}F -FLT is a marker of tumor proliferation and its uptake has been shown to be proportional to the DNA synthesis rate and proliferative indices [81].

Several small studies of lymphomas, lung cancer, and brain tumors suggest that ^{18}F -FDG is more sensitive for lesion detection; however ^{18}F -FLT may be more specific [82,83]. Other small series imply that ^{18}F -FLT may be especially valuable in predicting early response to therapy [84], as the imaging results are not complicated by the inflammation caused by therapy.

Oyama *et al.* [85] evaluated the ability of ^{18}F -FLT to assess early therapeutic effects of androgen deprivation in an animal tumor model of prostate cancer. In this study, sub-cutaneous tumor xenografts were created in athymic mice using the human androgen-dependent cell line CWR22. Biodistribution studies demonstrated that ^{18}F -FLT is rapidly taken up by the tumor and is retained longer than in other tissues. In addition, there was significant decrease in ^{18}F -FLT uptake in mice treated with the androgen deprivation drug diethylstilbestrol in comparison with control mice. Even though the authors concluded that ^{18}F -FLT may be useful in the evaluation of changes in the proliferation activity of prostate cancer during AD therapy, many questions remain. For example, the usefulness of ^{18}F -FLT for detection of skeletal metastases is still unclear since visualization of lesions may be hindered by prominent background activity in the bone marrow.

Radiolabeled Monoclonal antibodies

Radiolabeled monoclonal antibodies (mAb) directed against specific cell surface antigens have been extensively used in imaging and therapy of cancer [86]. The prostate specific membrane antigen (PSMA) is a good example of such a target. PSMA is a 100-kDa type 2 transmembrane glycoprotein expressed in prostate epithelial cells. PSMA is 94% extracellular and contains short internal and transmembrane domains [87]. Expression is low in normal prostate tissue but increases in both localized and metastatic prostate cancer. PSMA expression correlates well with tumor grade and is significantly up-regulated in androgen independent prostate cancer.

Gamma-scintigraphy with ^{111}In capromab pendetide (Prostascint®, Cytogen Corporation, Princeton, N.J.) is clinically approved by the FDA for pre-surgical staging or evaluation of biochemical recurrence after local therapy. ^{111}In capromab pendetide is a conjugated murine IgG1 mAb (7E11-C5.3) that recognizes the PSMA epitope localized in the intracellular domain of PSMA. Manyak *et al* studied 152 patients undergoing pelvic lymph node dissection classified as intermediate and high risk for lymph node metastases. The sensitivity and specificity for lymph node detection was 62% and 72% respectively. On the other hand, the

sensitivity of CT and MRI was only 4% and 15% respectively [88]. Elgamal *et al* evaluated patients with biochemical failure after radical prostatectomy, radiation therapy, and/or hormonal therapy. The authors reported a sensitivity of 89%, a specificity of 67%, and an overall accuracy of 89% [89]. Even though further studies demonstrate increased accuracy with CT or MRI and likely with modern hybrid SPECT/CT technology, enthusiasm for this compound remains guarded [90].

One of the major drawbacks with ^{111}In capromab pendetide imaging is that it is suboptimal for detection of bone metastases. In fact, capromab imaging is significantly less sensitive than bone scans [91]. Since the skeleton is the earliest and most common site of metastases, this method has limited clinical utility. The fundamental problem with ^{111}In capromab pendetide appears to be that the antibody targets the intracellular domain of PSMA and only binds dead or dying cells but fails to recognize viable cancer cells.

Contrary to ^{111}In capromab pendetide that targets the intracellular domain of PSMA, J591 (Millenium Pharmaceuticals, Cambridge, M.A.) is a humanized IgG1 mAb, that targets a binding site on the exterior of the cell. External epitopes improve availability of the antigen and thus lesion detectability [92]. Pandit-Taskar *et al*, investigated 14 patients with androgen independent prostate cancer [93]. ^{111}In labeled J591 localized 93.7% of skeletal lesions detected by conventional imaging. However, the detection rate for soft tissue lesions was low, possibly relating to the small size and locations of the lesions. The group at Cornell University has performed two Phase I trials evaluating the potential use of J591 as a therapeutic vector for radioimmunotherapy. In the first trial, ^{111}In -J591 was used as a surrogate label for imaging and biodistribution followed by therapy with the pure beta-emitter ^{90}Y -J591 conjugate [94]. A subsequent approach utilized ^{177}Lu -J591 which emits 15% of its energy as γ -emission in addition to the beta emissions, and can be used for imaging and therapy [95]. Thus, antibody imaging with targeting to the external domain of PSMA appears to have great prospects not only for diagnostic imaging but also for treatment of patients with metastatic prostate cancer.

Additional Promising Radiotracers

Additional radiotracers show potential in the evaluation of prostate cancer and warrant further investigation. These include the positron emitter radioisotopes ^{18}F -fluoride, ^{11}C -methionine, and ^{11}C -tyrosine [96-98]. The reader is referred to the NCI Molecular Imaging Database (MICAD): <http://www.ncbi.nlm.nih.gov/books/bookres.fcgi/micad/home.html>. This database currently contains 42 SPECT and 79 PET (as of 05/07/2008) which have been used in humans.

Conclusion

The role of molecular imaging in prostate cancer is continually evolving. New MRI techniques combined with new radiotracers that target not only glucose utilization but other specific tumor properties such as tumor proliferation, membrane turnover and amino acid transport can potentially stage, re-stage, and monitor treatment in patients with prostate cancer. Molecular imaging does not promise a “magic bullet”, but a new set of tools to understand cancer biology *in vivo*. It will not replace conventional methods but work synergistically. The challenge is to maximize the potential of each method employed.

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Figure 1.
Transrectal ultrasound image in the axial plane shows of the peripheral (P) and central (C) zones without evidence of a focal lesion.

Figure 2. Transrectal ultrasound image in axial plane demonstrates a hypoechoic triangular area in the anterior horn of the left peripheral zone that is suspicious for tumor (arrow).

Figure 3. Axial contrast enhanced computed tomography (CT) image of a patient with prostate cancer shows no evidence of tumor within prostate gland (arrow). CT has inherently low contrast resolution for the prostate and surrounding tissues.

Figure 4. Axial contrast enhanced computed tomography images of a patient with prostate cancer (PSA>50ng/ml) shows enlarged prostate gland with an infiltrative tumor lesion (arrows) (a) and distant mediastinal lymph node involvement (arrow) (b) (courtesy of Dr. Musturay Karcaaltincaba, Ankara, Turkey).

Figure 5.

Axial T2 weighted images demonstrates a normal peripheral zone (P) which is hyperintense compared to the transitional zone (T), and is separated by a pseudocapsule (arrowheads); additionally the true capsule of the prostate gland is seen as a hypointense rim around the gland (solid arrows) with neurovascular bundles at the posterolateral aspect of the capsule (dashed arrows) (b); normal seminal vesicles (arrows) are seen posterior to base of urinary bladder (UB) (b).

Figure 6. Axial (a) and sagittal (b) T2 weighted images of a patient with prostate cancer show focal low signal intensity lesion in the left mid peripheral zone (arrows) consistent with prostate cancer.

Figure 7.

Axial (a) and coronal (b) T2 weighted images of a patient with prostate cancer shows a tumor in the right mid peripheral zone with extracapsular extension (arrow); additionally a nodular low signal intensity focus invading the pseudocapsule consistent with transitional zone tumor is also seen (arrowheads).

Figure 8.

Axial (a) and coronal (b) T2 weighted images of a patient with prostate cancer depicts a tumor in the right peripheral zone (asterix). Tumor invades the capsule (arrowhead) and directly extends into the periprostatic space (arrow) (a); moreover tumor invades right obturator internus muscle (arrowhead) (b).

Figure 9. Axial T2 weighted image of a patient with prostate cancer shows a nodular low signal intensity lesion at the right apex peripheral zone (asterix) with ipsilateral capsular bulge and obliteration of recto-prostatic angle (arrow).

Figure 10. Sagittal T2 weighted image of a patient with prostate cancer demonstrates a big peripheral zone tumor (asterix) which extends superiorly and invades seminal vesicles (arrow).

Figure 11.

Axial T1 weighted image (a) of a patient who had TRUS guided sextant biopsy 5 weeks prior to the MRI which shows hyperintense foci consistent with hemorrhage (arrows); numerous low signal intensity foci secondary to hemorrhage mimicking cancers (arrows) are seen on axial T2 weighted image (b).

Figure 12.

Axial T2 weighted image of a patient with prostate cancer shows low signal intensity focus suspicious for tumor in the left peripheral zone (arrow) (a); Ktrans and Kep analysis of the corresponding slice performed with a two compartment kinetic model localizes the lesion to the left peripheral zone (arrows) (upper row). Comparison of the gadopentetate dimeglumine concentration versus time curves of the normal (right) and tumor (left) sites demonstrate that wash-in and wash-out processes were more rapid in the tumor (lower row).

Figure 13.

Flow chart shows Krebs cycle and citrate metabolism in normal prostate gland cell. In tumor cells zinc is missing, which leads to re-activation of aconitase that converts citrate to cis-aconitate, ultimately citrate is metabolized in the Krebs cycle instead of being stored, which results in depletion of citrate detected on MR spectroscopy.

Figure 14.

MR spectroscopy image and corresponding voxels demonstrate increased choline and diminished citrate peaks representing tumor (T) (voxels with asterix) at right peripheral zone (a); whereas normal side (N) at left peripheral zone contains normal voxels with normal choline and citrate peaks (b).

Figure 15.

Axial T2 weighted MR images of a patient with prostate cancer demonstrates bilateral low signal intensity foci suspicious for tumor (arrows) (a), suspicious lesions for cancer appear as bright and dark on corresponding raw diffusion weighted (b) and apparent diffusion coefficient (ADC) maps (c), respectively (arrows).

Figure 16.

65 year-old male with stage IV prostate cancer undergoing chemotherapy. Pre-treatment ^{18}F -FDG PET images (a) demonstrate multiple metabolic avid lesions throughout the skeleton. Post-treatment PET images (b) demonstrate interval resolution of the ^{18}F -FDG avid lesions. Pre-treatment and post-treatment bone scans (c and d) demonstrate little interval change (Courtesy of Dr. Steven M. Larson, Memorial Sloan-Kettering Cancer Center).

Figure 17.

64 year-old male with non-Hodgkins lymphoma. An incidental focus of increased ^{18}F -FDG uptake in the prostate prompted a biopsy which demonstrated infiltrating adenocarcinoma, gleason 7, stage T3a (courtesy Dr. Annemi Klopper, Cape PET-CT Centre, South Africa).

Figure 18.

Transaxial CT (a), PET (b), and fused (c) ^{18}F -FACBC PET/CT images in a patient with rising PSA status post radiation therapy. A focus of increased radiotracer uptake in the periphery of the right prostate gland helped guide biopsy. Transaxial CT (d), ^{111}In capromab SPECT (e), and fused SPECT/CT (f) images demonstrate no abnormal foci of radiotracer uptake. The patient was treated locally with cryotherapy (courtesy of Dr. David Schuster, Emory University).

Figure 19. Coronal PET (a), Transaxial PET (b), Transaxial CT (c), and fused PET/CT (d) ^{18}F -FDHT images in a patient with metastatic prostate cancer demonstrated several foci of increased radiotracer uptake in the skeleton (courtesy of Dr. Heiko Schoder, Memorial Sloan-Kettering Cancer Center).