Published in final edited form as:
Mol Imaging. 2009 ; 8(2): 56–64.

Molecular Imaging of Prostate Cancer: A Concise Synopsis

Hossein Jadvar
USC Molecular Imaging Center, Department of Radiology, Keck School of Medicine, University of Southern California, Los Angeles, CA.

Abstract

Prostate cancer is the most common malignancy in men and continues to be a major public health problem. Imaging of prostate cancer remains particularly challenging owing to disease heterogeneity. Molecular imaging can provide unprecedented opportunities for deciphering the molecular mechanisms that are involved in the development and natural progression of prostate cancer from a localized process to the hormone-refractory metastatic disease. Such understanding will be the key for targeted imaging and therapy and for predicting and evaluating treatment response and prognosis. In this article, we review briefly the contribution of multimodality molecular imaging methods for the in vivo characterization of the pathophysiology of prostate cancer.

PROSTATE CANCER is the most common cancer and the second leading cause of cancer death affecting men in the United States. As life expectancy increases, so will the incidence of this disease, creating what will become a major public health problem. Prostate cancer is clinically a heterogeneous disease characterized by biologic behavior that ranges between indolent and aggressive states. The exact molecular basis for the observed disease heterogeneity is not well understood.

Molecular imaging is a general term that refers to the merging of molecular biology and the advances in imaging techniques and probe design for monitoring directly or indirectly the spatiotemporal distribution of molecular or cellular processes for biochemical, biologic, diagnostic, or therapeutic applications.1 Imaging can provide unique opportunities not only for interrogating in vivo the underlying molecular mechanisms that are involved in the development and progression of prostate cancer but also for optimizing targeted therapy and for predicting and evaluating treatment response.

In this article, we briefly discuss the molecular and genetic alterations in prostate cancer and then review the major conceptual contribution of various imaging modalities for the in vivo characterization of prostate cancer. The imaging modality–based organization of information not only achieves a balance between presentations of the relevant biomarkers but also clearly highlights how these studies have been performed. The reader is encouraged to refer to the relevant bibliography for additional detailed information.

Molecular Biomarkers

Prostate cancer is probably the final product of complex interactions of a number of genetic and molecular abnormalities. Many factors have also been observed to potentially increase

Address reprint requests to: Hossein Jadvar, MD, PhD, MPH, MBA, Department of Radiology, Keck School of Medicine, University of Southern California, 2250 Alcazar Street, CSC 102, Los Angeles, CA 90033; e-mail: jadvar@usc.edu..

Financial disclosure of reviewers: None reported.

(eg, vasectomy, chronic prostatitis, obesity, diet, smoking) or decrease (alcohol, cirrhosis, diabetes mellitus, selenium, zinc, vitamins D and E, nonsteroidal antiinflammatory drugs, soy, lycopene, green tea) the risk for prostate cancer.2 Relatively extensive work has been done to date to characterize the molecular and genetic profile of prostate cancer that could be developed into various molecular imaging approaches.3–14 These include but are not limited to mutations and/or amplifications of oncogenes (*BCL2*, c-*myc*, *HER2*), genes encoding for metabolism of androgen, androgen receptor (AR) and coregulators, AR-regulated genes (eg, gonadotropin-releasing hormone [Gn-RH] receptors), and deletions or loss of expression of tumor suppressor genes (*p27*, *p53*, *PTEN*, *GSTP1*). For example, *PTEN* inactivation (phosphatase and tensin homologue deleted on chromosome 10), which has been noted to be associated with high-grade prostate tumors and with tumor progression, may exert its effect through upregulation of cell cycle genes such as *cdc6* and cyclin E2, which, in turn, potentiate metastatic disease.15 Other genetic and molecular abnormalities may include *CYP17* (encoding cytochrome P-450c17α, which is responsible for testosterone synthesis), *SRD5A2* (encoding 5α-reductase isoenzyme, which converts testosterone to the more potent dihydrotestosterone), HPC1/RANSEL (a ribonuclease that degrades ribonucleic acid [RNA]), c-Kit/tyrosine kinase receptor (activator of the Src family of tyrosine kinases), hespin (a type II transmembrane serine protease), EPCA (early prostate cancer antigen that is a nuclear matrix protein), and vitamin D receptor.2 Recently, it has been observed that induction and upregulation of stress response protein GRP78 (78 kDa glucose regulated protein) are associated with the development and survival of castration-resistant prostate cancer cells in an androgen-deficient microenvironment.16,17

Serum prostate-specific antigen (PSA) has long been used as an organ-specific marker and is currently the most commonly used marker for prostate cancer. PSA is a 33 kDa androgen-regulated serine protease that is produced by the prostate gland. Age-specific normal ranges have been determined because the standard PSA reference range of 0.0 to 0.4 ng/mL does not account for age and volume changes in relation to benign prostatic hyperplasia (BPH).2 However, PSA and other related parameters (eg, PSA density, PSA velocity, free and complexed PSA) have limited sensitivity (may be undetectable or low even in disseminated disease) and limited specificity (a high level with benign disease) for prostate cancer, cannot localize the disease if present, may be affected in a manner unrelated to the impact of therapy on tumor, and are the cause of great anxiety and overstated diagnostic expectations by the patient, coined “PSA-itis.”18–20 Another relevant prostate biomarker is the prostate-specific membrane antigen (PSMA), which is a glycoprotein expressed in both the benign and the neoplastic prostatic epithelial cells and in other tissues, such as kidney, liver, and brain.21,22 It is upregulated in hormone-resistant states and in metastatic disease.22,23

Androgens are also essential for the development, growth, and maintenance of the prostate. The effects of androgens are exerted via the nuclear AR, which is a ligand-dependent (either testosterone or 5α-dihydrotestosterone) transcription activator involved in cellular proliferation and differentiation and is present in all histologic types of prostate tumors, in recurrent carcinoma, and in tumor metastases.24,25 Most patients respond favorably to androgen ablation, but nearly all patients will relapse to the castration-resistant clinical state that may be due to AR mutation or aberrant function (eg, receptor activation in a ligand-independent manner), amplification of coactivators, activation of oncogenes, and autocrine growth factor stimulation.26

Magnetic Resonance Imaging and Magnetic Resonance Spectroscopy

Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) have been employed in the detection and characterization of prostate cancer.27–29 Dynamic contrast-enhanced MRI with small-molecular-weight gadolinium chelates and higher-molecular-

weight P792 have been studied.30,31 Despite the observation of a slower washout rate of the contrast agent from metastatic tumors than nonmetastatic tumors, generally significant limitations and overlap have been noted in relation to differential characterization with benign conditions such as prostatitis and BPH.32 Recent reports of using lymphotropic super-paramagnetic nanoparticles in conjunction with high-resolution MRI may allow the detection of small and otherwise undetectable lymph node metastases in patients with prostate cancer.33 However, the exact clinical utility of such a diagnostic imaging approach remains to be determined.

In one study, prostate cancer cells were directly imaged using an intracellular MRI contrast agent that was designed by using the c-*myc* messenger ribonucleic acid (mRNA)-specific peptide nucleic acid as a "retention" contrast agent.34 Researchers at Harvard Medical School studied the gene expression profile underlying the magnetic resonance–derived imaging and MRS-derived spectral features of prostate cancer.35 The RNA expression profiles were obtained from the Affymetrix Gene Chip microarrays and quantitative reverse transcriptase polymerase chain reaction analysis. An overexpression of choline kinase was noted in the majority of primary tumors and neuropeptide Y (an angiogenic factor) in a subset of prostate tumors visualized on dynamic contrast-enhanced MRI. In another related study for assessing gene expression in vivo, the proof of principle work for using [^{19}F] MRS for assessing β-galactosidase activity was reported demonstrating the ability to differentiate wild-type from *lacZ* gene (encoding β-galactosidase) expressing androgen-independent PC3 prostate tumor xenografts in mice.36 These studies illustrate the correlation of MRI and MRS parameters to the underlying molecular events in prostate cancer.

In another work, biotinylated anti-PSMA antibody was conjugated to streptavidin-labeled iron oxide nanoparticles for MRI detection of prostate cancer cells.37 T_1-weighted signal was greater for cells with magnetic particles bound to cell surface than for cells that internalized the particles, whereas no such effect was noted with T_2-weighted images. MRI-derived functional diffusion maps have also been found to be useful in assessing treatment response in a preclinical model of prostate cancer bone metastasis.38 The functional diffusion map demonstrated an increase in water diffusion in relation to loss of tumor cell membrane integrity and density induced by successful therapy. Further clinical evaluation of this concept in comparison with standard imaging studies such as bone scintigraphy may provide a more sensitive imaging-based marker for early assessment of treatment response.

Single-Photon Emission Tomography and Positron Emission Tomography

Despite the relevance of PSMA in prostate cancer, Prostascint (Cytogen, Princeton, NJ), a radiolabeled antibody targeted to the PSMA, has been found to have several significant shortcomings, including limited predictive value in imaging the prostate fossa, particularly following radiation therapy, and low sensitivity for detecting osseous metastases; Prostascint is also technically demanding and requires interpretation at sites with experience and expertise.39 Recently, investigators from Johns Hopkins University presented the preparation of radiolabeled small-molecule ligands for PSMA ([^{125}I]DCIT, [^{11}C]DCMC, [^{18}F]DCFBC], as well as seven technetium 99m- or rhenium-labeled chelating agents attached to an amino-functionalized PSMA inhibitor with or without a variable length linker moiety.40-42 These efforts were based on potential capitalization on PSMA as a relevant biologic target for imaging and therapy of prostate cancer.

Positron emission tomography (PET) with [^{18}F]-fluorodeoxyglucose (FDG) is a molecular imaging technique that monitors tissue glucose metabolism, taking advantage of the long-known phenomenon that most tumors are hypermetabolic with increased glucose metabolism (Warburg effect). The upregulation of glucose transporter (GLUT) proteins

(primarily GLUT1 and/or GLUT3) and/or increased hexokinase (HK) enzymatic level and activity (primarily HK-II) have been observed in many cancers.[43-45] GLUT is the first rate-limiting step for glucose metabolism that allows energy-independent glucose transport across the cell membrane down the concentration gradient, whereas HK-II efficiently phosphorylates glucose to glucose-6-phosphate. Similar to glucose, FDG is phosphorylated to FDG-6-phosphate, but contrary to glucose-6-phosphate, it cannot be metabolized further in the glycolytic pathway and becomes trapped in the cell owing to its negative charge.[43-45] Few studies have reported specifically on expression of GLUTs in human prostate cancer. In one investigation, the GLUT1 mRNA expression was assessed by Northern blot analysis in the androgen-independent cell lines DU145 and PC3 and the androgen-sensitive LNCaP prostate cancer cell line.[46] Although GLUT1 expression was detected in all three cell lines, the level of expression was higher in the poorly differentiated cell lines DU145 and PC3 than in the well-differentiated hormone-sensitive LNCaP cell line, suggesting that the level of GLUT1 expression increases with progression of malignancy grade. Another study from Australia showed the expression of GLUT12 in human prostate cancer cell lines with its potential implication on enhanced glucose metabolism in prostate tumor.[47] Recently, British investigators evaluated the expression of a number of hypoxia-associated genes within BPH and prostate cancer (Gleason score 5−10) human tissue specimens.[48] *GLUT1* gene expression was significantly higher in prostate cancer than in BPH and was correlated directly with Gleason score ($R = .274$, $p = .026$). These findings may explain not only the observation of higher FDG accumulation in the castration-resistant (androgen-independent) tumors in comparison with castration-sensitive tumors but also the modulatory effect of androgen on the glucose metabolism of the castration-sensitive tumors.[49]

Two non-FDG PET tracers (^{11}C- or ^{18}F-labeled acetate and choline) have been relatively extensively studied in prostate cancer.[50-52] The cellular retention of ^{11}C acetate in prostate cancer cell lines is primarily due to incorporation of the radiocarbon into phosphatidylcholine and neutral lipids of the cells.[53,54] It has been suggested that fatty acid metabolism rather than glycolysis may be dominant in prostate cancer in view of alteration in several enzymes involved in the metabolism of fatty acids and enhanced beta-oxidation pathway.[55] Recent studies confirmed the involvement of the fatty acid synthesis pathway in ^{11}C acetate uptake in prostate tumors as an imaging marker for fatty acid synthase expression.[56] Fatty acid synthase is the major enzyme required for converting carbohydrates to fatty acids, and its upregulation plays a role in tumorigenesis of the prostate in the transgenic adenocarcinoma of mouse prostate (TRAMP) model.[57]

The biologic basis for radiolabeled choline uptake in tumors is the malignancy-induced upregulation of choline kinase, which leads to the incorporation and trapping of choline in the form of phosphatidylcholine (lecithin) in the tumor cell membrane.[58] Choline uptake in prostate tumor appears to be uncorrelated to cellular proliferation (as depicted by Ki-67) but may be affected by hypoxia.[59,60] It has also been demonstrated that under aerobic conditions, both androgen-sensitive and androgen-independent prostate tumors show higher choline uptake than that with radiolabeled acetate or with FDG. However, during hypoxia, the tumor uptake with FDG and acetate is higher than that with choline.[59] Furthermore, recent work has suggested that the uptake time interval and castration do not appear to significantly affect the level of radiolabeled choline uptake by the human prostate cancer xenograft.[61]

Recently, [^{11}C]acetoacetate has also been evaluated as a potential PET tracer of ketone body use by prostate tumors.[62] It was shown that PC-3 androgen-independent prostate tumors display moderate uptake of [^{11}C]acetoacetate with rapidly decreasing background activity. Further research would be needed to determine the exact biologic relevance of imaging

ketone body use to the natural history of prostate cancer and how it may be useful in a specific clinical setting.

With respect to the AR imaging, PET tracers such as 16β-^{18}F-fluoro-5α-dihydrotestosterone (^{18}F-FDHT) targeted to the AR have been developed and evaluated.63,64 Metabolism of ^{18}F-FDHT was rapid, with 80% conversion within 10 minutes to radiolabeled metabolites bound to plasma proteins. The tracer uptake level in prostate tumors was also demonstrated to decrease significantly in response to androgen ablation therapy, supporting the receptor-mediated process of ^{18}FFDHT uptake.65 It has also been shown that pharmacologic AR inhibition (eg, flutamide) and androgen withdrawal exert their therapeutic effects in androgen-dependent tumors through different molecular mechanisms.66 Interestingly, the antiandrogenic effect of treatment appears to decrease glucose metabolism in prostate cancer, which then can be monitored with FDG or used to potentially predict the development of castration-resistant disease.49 Other androgen-related agents have also been synthesized to explore the effect of the sex hormone–binding globulin in the target tissue uptake of AR radiotracers.67,68

It has been noted that some tumors, including prostate cancer (mostly androgen-independent), overexpress gastrin-releasing peptide (GRP) receptors. Radiolabeled bombesin (a neuropeptide with high affinity for GRP receptors) analogues have been synthesized and evaluated for single-photon emission computed tomography (SPECT) (^{111}In label) and PET (^{64}Cu or ^{18}F label) visualization of prostate cancer.69-71 Whether imaging the GRP receptor is deemed clinically useful will need further investigation in relation to various stages and markers of the disease.

In relation to tumor angiogenesis, the vascular endothelial growth factor signaling pathway and the integrin $\alpha_v\beta_3$ (a cell adhesion molecule) have been identified to play key roles. Molecular imaging of these targets in the tumor vasculature may help tailor targeted antiangiogenic therapy.72,73 A number of PET tracers suitable for integrin receptor imaging have been reported that demonstrate high specificity in various types of tumors, including prostate cancer models.74 However, active research continues in identifying more specific biologic markers for interrogating the tumor vessels. These investigations will not only shed more light on the biologic basis of the complex signals involved in malignancy-induced angiogenesis but may also help facilitate the design and image-based testing of drugs targeted to tumor-specific angiogenesis.

Singh and colleagues recently reviewed various strategies for molecular imaging of reporter gene expression in prostate cancer.75 These methods involve the introduction of a reporter gene into the target cell via a particular vehicle (viral or nonviral) with the gene expressed by a particular promoter. The promoter may be tissue specific, inducible, or constitutive. The ultimate reporter protein product (eg, enzyme, receptor) then interacts with the appropriate reporter probe, producing an imaging signal that becomes available for detection. When the reporter gene is combined with a therapeutic (suicide) gene, tissue-specific (prostate tumor) expression of the therapeutic gene may be inferred through the expression of the reporter gene as interrogated by the reporter probe.76 The overall goal of these strategies is to monitor in vivo the successful delivery and spatiotemporal expression of the therapeutic gene. An example of such a strategy is the PET imaging of the adenovirus-delivered herpes simplex virus thymidine kinase (*HSV-tk*) reporter gene in conjunction with the ^{18}F-FHBG reporter probe.77

Recent work has shown improved target specificity for delivery and expression of the therapeutic gene in prostate cancer bone metastases.78 In this study, dual-targeted lentiviral vectors were developed that interact with prostate stem cell antigen expressed on prostate

cancer cells with transcriptional specificity mediated by a prostate cell–specific promoter. Strategies such as two-step transcriptional amplification–based lentiviral vector have also been reported to facilitate appropriate in vivo targeting of prostate cancer after systemic administration of the vector that is considered a valuable component in the eventual adoption of gene therapy protocols.[79-82] Another mechanism involves exogenous transfection of prostate cancer cells with the Na/I symporter (a plasma membrane glycoprotein involved in active thyroid iodine uptake) that allows tumor killing through radioiodine therapy.[83]

Sentinel lymph node (SLN) technique for staging has been used for many cancers, in particular melanoma and breast cancer. Investigators from UCLA extended this general technique for directly imaging SLN metastasis in prostate cancer.[84] In this work, the lymphotropic recombinant human adenoviral vectors were used containing prostate-restricted expression of optical and PET reporter genes. The peritumoral administration of the vector allowed direct visualization of reporter gene expression in SLN metastases. Bone is also a common site of metastatic disease in prostate cancer. Whole-body ^{18}F-fluoride ion micro-PET has been used to serially monitor the tumor development and response to treatment in mouse models of prostate cancer osseous metastatic disease, and when combined with micro-CT, correlative structural changes could also be interrogated.[85]

Optical Imaging

Engineered mouse models of prostate cancer have been developed in conjunction with imaging markers to allow in vivo monitoring of tumor growth at different stages of the disease and to facilitate the translation of the mouse studies into human clinical trials.[86-90] In one model, for example, the feasibility of generating bigenic mice by crossbreeding the sPSA-Luc transgenic mouse model (with luciferase gene expression restricted to the prostate under control of the supra PSA promoter) with the TRAMP model.[87] These animal models may provide the platform for in vivo imaging of prostate cancer progression from a localized process to the disseminated state.

It has been noted that increased expression of a splice variant of the Kruppel-like factor tumor suppressor gene (*KLF6-SV1*) in the excised prostate tumor predicts poor prognosis and earlier time to recurrence. This gene is also upregulated in hormone-refractory metastatic prostate cancer. Bioluminescent imaging (BLI) in mouse models of prostate cancer has been used to demonstrate that *KLF6-SV1* overexpression is associated with increased propensity for metastatic spread to lymph nodes, whereas there is little effect on localized tumor growth.[91] Similarly, exogenous hepsin expression also negatively regulates cell growth in metastatic prostate cancer cell lines, which may link the decrease in or loss of hepsin expression to poor prognosis.[92] Imaging probes for hepsin have been developed by conjugating multiple peptides to fluorescent nanoparticles that bind specifically to hespin-expressing prostate cancer xenografts.[93] In another investigation, in vivo quantitative BLI was used to document the liposome-encapsulated human alphav-siRNA (small interfering RNA) inhibition of the growth of luciferase-tagged PC3 (androgen-independent) prostate cancer in bone.[94] These interesting observations may provide potential methods for an imaging-based prediction and evaluation of metastatic prostate cancer.

Multifunctional nanometer probes based on semiconductor quantum dots may also offer a viable tool for molecular diagnostic imaging and therapy in prostate cancer.[95] In particular, multiplexed imaging of specific molecular targets with appropriate background noise reduction (eg, autofluoresence) and weak spectral signal amplification may be achieved in vivo.[96] The utility of such a platform for in vivo targeting of human prostate cancer in a nude mouse model has been demonstrated with both passive tumor targeting (permeation

and retention) and active tumor targeting (through antibody binding to specific cell surface antigens).97,98

Summary

We briefly reviewed the underlying molecular and genetic alterations in prostate cancer and the current evidence on the emerging role of multimodality imaging in molecular profiling and characterization of this major public health problem. Molecular imaging will pave the way for direct translation of findings in animal models to the care of men with prostate cancer.

Acknowledgments

Financial disclosure of authors: Hossein Jadvar was supported by National Institutes of Health/National Cancer Institute R01-CA111613.

References

1. Thakur M, Lentle BC. Report of a summit on molecular imaging. Radiology. 2005; 236:753–5. [PubMed: 16118158]
2. Abdel-Wahab, M.; Silva, OE. Prostate cancer: a practical guide. Saunders Elsevier; Philadelphia: 2008.
3. Richardson AM, Woodson K, Wang Y, et al. Global analysis of prostate cancer-associated stroma and epithelia. Diagn Mol Pathol. 2007; 16:189–97. [PubMed: 18043281]
4. Biancolella M, Valentini A, Minella D, et al. Effects of dutasteride on the expression of genes related to androgen metabolism and related pathway in human prostate cancer cell lines. Invest New Drugs. 2007; 25:491–7. [PubMed: 17636412]
5. Gelmann EP, Semmes OJ. Expression of genes and proteins specific for prostate cancer. J Urol. 2004; 172(5 Pt 2):S23–6. [PubMed: 15535438]
6. Carnell DM, Smith RE, Daley FM, et al. Target validation of cytochrome P450 CYP1B1 in prostate carcinoma with protein expression in associated hyperplastic and premalignant tissue. Int J Radiat Oncol Biol Phys. 2004; 58:500–9. [PubMed: 14751521]
7. Trotman LC, Niki M, Dotan ZA, et al. Pten dose dictates cancer progression in the prostate. PLoS Biol. 2003; 1:E59. [PubMed: 14691534]
8. Karam JA, Mason RP, Koeneman KS, et al. Molecular imaging of prostate cancer. J Cell Biochem. 2003; 90:473–83. [PubMed: 14523981]
9. Rashid MG, Sanda MG, Vallorosi CJ, et al. Posttranslational truncation and inactivation of human E-cadherin distinguishes prostate cancer from matched normal prostate. Cancer Res. 2001; 61:489–92. [PubMed: 11212238]
10. Hubert RS, Vivanco I, Chen E, et al. STEAP: a prostate-specific cell-surface antigen highly expressed in human prostate tumors. Proc Natl Acad Sci U S A. 1999; 96:14523–8. [PubMed: 10588738]
11. Fernandez-Pol JA, Fletcher JW, Hamilton PD, et al. Expression of metallopanstimulin and oncogenesis in human prostatic carcinoma. Anticancer Res. 1997; 17:1519–30. [PubMed: 9179190]
12. Hamdy FC, Fadlon EJ, Cottom D, et al. Matrix metalloproteinase 9 expression in primary human prostatic adenocarcinoma and benign prostatic hyperplasia. Br J Cancer. 1994; 69:177–82. [PubMed: 7506923]
13. Darby S, Stockley J, Khan MM, et al. Expression of GnRH type II is regulated by the androgen receptor in prostate cancer. Endocr Relat Cancer. 2007; 14:613–24. [PubMed: 17914092]
14. Uetsuki H, Tsunemori H, Taoka R, et al. Expression of a novel biomarker, EPCA, in adenocarcinomas and precancerous lesions in the prostate. J Urol. 2005; 174:514–8. [PubMed: 16006883]

15. Wu Z, Cho H, Hampton GM, et al. Cdc6 and cyclin E2 are PETN-regulated genes associated with human prostate cancer metastasis. Neoplasia. 2009; 11:66–76. [PubMed: 19107233]
16. Pootrakul L, Datar RH, Shi SR, et al. Expression of stress response protein GRP78 is associated with the development of castration-resistant prostate cancer. Clin Cancer Res. 2006; 12(20 Pt 1): 5987–93. [PubMed: 17062670]
17. Daneshmand S, Quek ML, Lin E, et al. Glucose-regulated protein GRP78 is upregulated in prostate cancer and correlates with recurrence and survival. Hum Pathol. 2007; 38:1547–52. [PubMed: 17640713]
18. Beardo P, Fernandez PL, Corral JM, et al. Undetectable prostate specific antigen in disseminated prostate cancer. J Urol. 2001; 166:993. [PubMed: 11490269]
19. Dreicer R. Metastatic prostate cancer: assessment of response to systemic therapy. Semin Urol Oncol. 1997; 15:28–32. [PubMed: 9050137]
20. Lofters A, Juffs HG, Pond GR, et al. “PSA-itis”: knowledge of serum prostate specific antigen and other causes of anxiety in men with metastatic prostate cancer. J Urol. 2002; 168:2516–20. [PubMed: 12441952]
21. O'Keefe DS, Bacich DJ, Heston WD. Comparative analysis of prostate-specific membrane antigen (PSMA) versus a prostate-specific membrane antigen-like gene. Prostate. 2004; 58:200–10. [PubMed: 14716746]
22. Fair WR, Israeli RS, Heston WD. Prostate-specific membrane antigen. Prostate. 1997; 32:140–8. [PubMed: 9215402]
23. Elgamal AA, Holmes EH, Su SL, et al. Prostate-specific membrane antigen (PSMA): current benefits and future value. Semin Surg Oncol. 2000; 18:10–6. [PubMed: 10617892]
24. Culig Z, Hobisch A, Hittmair A, et al. Androgen receptor gene mutations in prostate cancer. Implications for disease progression and therapy. Drugs Aging. 1997; 10:50–8. [PubMed: 9111707]
25. Culig Z, Klocker H, Bartsch G, et al. Androgen receptors in prostate cancer. Endocr Relat Cancer. 2002; 9:155–70. [PubMed: 12237244]
26. Jenster G. The role of the androgen receptor in the development and progression of prostate cancer. Semin Oncol. 1999; 26:407–21. [PubMed: 10482183]
27. Kurhanewicz J, Swanson MG, Nelson SJ, et al. Combined magnetic resonance imaging and spectroscopic imaging approach to molecular imaging of prostate cancer. J Magn Reson Imaging. 2002; 16:451–63. [PubMed: 12353259]
28. Song SK, Ou Z, Grabedian EM, et al. Improved magnetic resonance imaging detection of prostate cancer in a transgenic mouse model. Cancer Res. 2002; 62:1555–8. [PubMed: 11888935]
29. Gossmann A, Okuhata Y, Shames DM, et al. Prostate cancer tumor grade differentiation with dynamic contrast-enhanced MR imaging in the rat: comparison of macromolecular and small-molecular contrast media—preliminary results. Radiology. 1999; 213:265–72. [PubMed: 10540670]
30. Fan X, Medved M, River JN, et al. New model for analysis of dynamic contrast-enhanced MRI data distinguishes metastatic from nonmetastatic transplanted rodent prostate tumors. Magn Reson Med. 2004; 51:487–94. [PubMed: 15004789]
31. Kim YR, Savellano MD, Weissleder R, et al. Steady-state and dynamic contrast MR imaging of human prostate cancer xenograft tumors: a comparative study. Technol Cancer Res Treat. 2002; 1:489–95. [PubMed: 12625776]
32. Alonzi R, Padhani AR, Allen C. Dynamic contrast enhanced MRI in prostate cancer. Eur J Radiol. 2007; 63:335–50. [PubMed: 17689907]
33. Harisinghani MG, Barentsz JO, Hahn PF, et al. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. N Engl J Med. 2003; 348:2491–9. [PubMed: 12815134]
34. Heckl S, Pipkorn R, Waldeck W, et al. Intracellular visualization of prostate cancer using magnetic resonance imaging. Cancer Res. 2003; 63:4766–72. [PubMed: 12941791]
35. Lenkinski RE, Bloch BN, Liu F, et al. An illustration of the potential for mapping MRI/MRS parameters with genetic over-expression profiles in human prostate cancer. MAGMA. 2008; 21:411–21. [PubMed: 18752015]

36. Liu L, Kudibagkar VD, Yu JX, et al. 19F-NMR detection of lacZ gene expression via the enzymic hydrolysis of 2-fluoro-4-nitrophenyl beta-D-galactopyranoside in vivo in PC3 prostate tumor xenografts in the mouse. FASEB J. 2007; 21:2014–9. [PubMed: 17351127]
37. Serda RE, Adolphi NL, Bisoffi M, et al. Targeting and cellular trafficking of magnetic nanoparticles for prostate cancer imaging. Mol Imaging. 2007; 6:277–88. [PubMed: 17711783]
38. Lee KC, Sud S, Meyer CR, et al. An imaging biomarker of early treatment response in prostate cancer that has metastasized to the bone. Cancer Res. 2007; 67:3524–8. [PubMed: 17440058]
39. Haseman MK, Rosenthal SA, Polascik TJ. Capromab pendetide imaging of prostate cancer. Cancer Biother Radiopharm. 2000; 15:131–40. [PubMed: 10803318]
40. Foss CA, Mease RC, Fan H, et al. Radiolabeled small-molecule ligands for prostate-specific membrane antigen: in vivo imaging in experimental models of prostate cancer. Clin Cancer Res. 2005; 11:4022–8. [PubMed: 15930336]
41. Banerjee SR, Foss CA, Castanares M, et al. Synthesis and evaluation of technetium-99m- and rhenium-labeled inhibitors of the prostate-specific membrane antigen (PSMA). J Med Chem. 2008; 51:4504–17. [PubMed: 18637669]
42. Mease RC, Dusich CL, Foss CA, et al. N-[N-[(S)-1,3-Dicarboxypropyl]carbamoyl]-4-[18F]fluorobenzyl-L-cysteine, [18F]DCFBC: a new imaging probe for prostate cancer. Clin Cancer Res. 2008; 14:3036–43. [PubMed: 18483369]
43. Macheda ML, Rogers S, Bets JD. Molecular and cellular regulation of glucose transport (GLUT) proteins in cancer. J Cell Physiol. 2005; 202:654–62. [PubMed: 15389572]
44. Mathupala SP, Ko YH, Pederson PL. Hexokinase II: cancer's double-edged sword acting as both facilitator and gatekeeper of malignancy when bound to mitochondria. Oncogene. 2006; 25:4777–86. [PubMed: 16892090]
45. Smith TA. Mammalian hexokinases and their abnormal expression in cancer. Br J Biomed Sci. 2000; 57:170–8. [PubMed: 10912295]
46. Effert P, Beniers AJ, Tamimi Y, et al. Expression of glucose transporter 1 (GLUT-1) in cell lines and clinical specimen from human prostate adenocarcinoma. Anticancer Res. 2004; 24:3057–63. [PubMed: 15517916]
47. Chandler JD, Williams ED, Slavin JL, et al. Expression and localization of GLUT1 and GLUT12 in prostate carcinoma. Cancer. 2003; 97:2035–42. [PubMed: 12673735]
48. Stewardt GD, Gray K, Pennington CJ, et al. Analysis of hypoxia-associated gene expression in prostate cancer: lysyl oxidase and glucose transporter 1 expression correlate with Gleason score. Oncol Rep. 2008; 20:1561–7. [PubMed: 19020742]
49. Jadvar H, Li X, Shahinian A, et al. Glucose metabolism of human prostate cancer mouse xenografts. Mol Imaging. 2005; 4:91–7. [PubMed: 16105512]
50. Ponde DE, Dence CS, Oyama N, et al. 18F-Fluoroacetate: a potential acetate analog for prostate tumors imaging—in vivo evaluation of 18F-fluoroacetate versus 11C-acetate. J Nucl Med. 2007; 48:420–8. [PubMed: 17332620]
51. Sutinen E, Nurmi M, Roivainen A, et al. Kinetics of [(11C)]choline uptake in prostate cancer: a PET study. Eur J Nucl Med Mol Imaging. 2004; 31:317–24. [PubMed: 14628097]
52. DeGrado TR, Coleman RE, Wang S, et al. Synthesis and evaluation of 18F-labeled choline as an oncologic tracer for positron emission tomography: initial findings in prostate cancer. Cancer Res. 2001; 61:110–7. [PubMed: 11196147]
53. Yoshimoto M, Waki A, Yonekura Y, et al. Characterization of acetate metabolism in tumor cells in relation to cell proliferation: acetate metabolism in tumor cells. Nucl Med Biol. 2001; 28:117–22. [PubMed: 11295421]
54. Shreve PD, Lannone P, Weinhold P. Cellular metabolism of [1-C14]-acetate in prostate cancer cells in vitro [abstract]. J Nucl Med. 2002; 43(5 Suppl):272P.
55. Liu Y. Fatty acid oxidation is a dominant bioenergetic pathway in prostate cancer. Prostate Cancer Prostatic Dis. 2006; 9:230–4. [PubMed: 16683009]
56. Vavere AL, Kridel SJ, Wheeler FB, et al. 1-11C-Acetate as a PET radiopharmaceutical for imaging fatty acid synthase expression in prostate cancer. J Nucl Med. 2008; 49:327–34. [PubMed: 18199615]

57. Pflug BR, Pecher SM, Brink AW, et al. Increased fatty acid synthase expression and activity during progression of prostate cancer in the TRAMP model. Prostate. 2003; 57:245–54. [PubMed: 14518031]
58. Zheng QH, Gradner TA, Raikwar S, et al. [11C]Choline as a PET biomarker for assessment of prostate cancer tumor models. Bioorg Med Chem. 2004; 12:2887–93. [PubMed: 15142549]
59. Hara T, Bansal A, DeGrado TR. Effect of hypoxia on the uptake of[methyl-3H]choline, [1−14C]acetate and [18F]FDG in cultured prostate cancer cells. Nucl Med Biol. 2006; 33:977–84. [PubMed: 17127170]
60. Breeuwsma AJ, Pruim J, Jongen MM, et al. In vivo uptake of [11C]choline does not correlate with cell proliferation in human prostate cancer. Eur J Nucl Med Mol Imaging. 2005; 32:668–73. [PubMed: 15765234]
61. Jadvar H, Gurbuz A, Li X, et al. Choline autoradiography of human prostate cancer xenograft: effect of castration. Mol Imaging. 2008; 7:147–52. [PubMed: 19123985]
62. Authier S, Tremblay S, Dumulon V, et al. [11c]Acetoacetate utilization by breast and prostate tumors: a PET and biodistribution study in mice. Mol Imaging Biol. 2008; 10:217–23. [PubMed: 18454299]
63. Larson SM, Morris M, Gunther I, et al. Tumor localization of 16beta-18F-fluoro-5alpha-dihydrotestosterone versus 18F-FDG in patients with progressive, metastatic prostate cancer. J Nucl Med. 2004; 45:366–73. [PubMed: 15001675]
64. Zanzonico PB, Finn R, Pentlow KS, et al. PET-based radiation dosimetry in man of 18F-fluorodihydrotestosterone, a new radiotracer for imaging prostate cancer. J Nucl Med. 2004; 45:1966–71. [PubMed: 15534070]
65. Dehdashti F, Picus J, Michalski JM, et al. Positron tomographic assessment of androgen receptors in prostate carcinoma. Eur J Nucl Med Mol Imaging. 2005; 32:344–50. [PubMed: 15726353]
66. Hagan R, Zhang LJ, Pottratz J, et al. Imaging androgen receptor function during flutamide treatment in the LAPC9 xenograft model. Mol Cancer Ther. 2005; 4:1662–9. [PubMed: 16275987]
67. Parent EE, Carlson KE, Katzenellenbogen JA. Synthesis of 7alpha-(fluoromethyl)dihydrotestosterone and 7alpha-(fluoromethyl)nortestosterone, structurally paired androgens designed to probe the role of sex hormone binding globulin in imaging androgen receptors in prostate tumors by positron emission tomography. J Org Chem. 2007; 72:5546–54. [PubMed: 17585812]
68. Garg S, Doke A, Black KW, et al. In vivo biodistribution of an androgen receptor avid PET imaging agent 7-alpha-fluoro-17 alpha-methyl-5-alpha-dihydrotestosterone ([(18F)F]FMDHT) in rats pretreated with cetrorelix, a GnRH antagonist. Eur J Nucl Med Mol Imaging. 2008; 35:379–85. [PubMed: 17934727]
69. de Visser M, Bernard HF, Erion JL, et al. Novel 111In-labeled bombesin analogues for molecular imaging of prostate tumors. Eur J Nucl Med Mol Imaging. 2007; 34:1228–38. [PubMed: 17287960]
70. Yang YS, Zhang X, Xiong Z, et al. Comparative in vitro and in vivo evaluation of two 64Cu-labeled bombesin analogs in a mouse model of human prostate adenocarcinoma. Nucl Med Biol. 2006; 33:371–80. [PubMed: 16631086]
71. Zhang X, Cai W, Cao F, et al. 18F-Labeled bombesin analogs for targeting GRP receptor-expressing prostate cancer. J Nucl Med. 2006; 47:492–501. [PubMed: 16513619]
72. Cai W, Chen X. Multimodality molecular imaging of tumor angiogenesis. J Nucl Med. 2008; 49(Suppl 2):113S–28S. [PubMed: 18523069]
73. Ocak I, Baluk P, Barrett T, et al. The biologic basis of in vivo angiogenesis imaging. Front Biosci. 2007; 12:3601–16. [PubMed: 17485324]
74. Zhang X, Xiong Z, Wu Y, et al. Quantitative PET imaging of tumor integrin alphavbeta3 expression with 18F-FRGD2. J Nucl Med. 2006; 47:113–21. [PubMed: 16391195]
75. Singh A, Massoud TF, Deroose C, et al. Molecular imaging of reporter gene expression in prostate cancer: an overview. Semin Nucl Med. 2008; 38:9–19. [PubMed: 18096460]

76. Johnson M, Sato M, Burton J, et al. Micro-PET/CT monitoring of herpes thymidine kinase suicide gene therapy in a prostate cancer xenograft: the advantage of a cell-specific transcriptional targeting approach. Mol Imaging. 2005; 4:463–72. [PubMed: 16285908]
77. Pantuck AJ, Berger F, Zisman A, et al. CLI-SR39: a noninvasive molecular imaging model of prostate cancer suicide therapy using positron emission tomography. J Urol. 2002; 168:1193–8. [PubMed: 12187266]
78. Pariente N, Morizono K, Virk MS, et al. A novel dual-targeted lentiviral vector leads to specific transduction of prostate cancer bone metastases in vivo after systemic administration. Mol Ther. 2007; 15:1973–81. [PubMed: 17653099]
79. Zhang L, Adams JY, Billick E, et al. Molecular engineering of a two-step transcription amplification (TSTA) system for transgene delivery in prostate cancer. Mol Ther. 2002; 5:223–32. [PubMed: 11863411]
80. Iyer M, Salazar FB, Lewis X, et al. Noninvasive imaging of enhanced prostate-specific gene expression using a two-step transcriptional amplification-based lentivirus vector. Mol Ther. 2004; 10:545–52. [PubMed: 15336654]
81. Iyer M, Salazar FB, Wu L, et al. Bioluminescence imaging of systemic tumor targeting using a prostate-specific lentiviral vector. Hum Gene Ther. 2006; 17:125–32. [PubMed: 16409131]
82. Wu L, Sato M. Integrated, molecular engineering approaches to develop prostate cancer gene therapy. Curr Gene Ther. 2003; 3:452–67. [PubMed: 14529351]
83. Dadachova E, Carrasco N. The Na/I symporter (NIS): imaging and therapeutic applications. Semin Nucl Med. 2004; 34:23–31. [PubMed: 14735456]
84. Burton JB, Johnson M, Sato M, et al. Adenovirus-mediated gene expression imaging to directly detect sentinel lymph node metastasis of prostate cancer. Nat Med. 2008; 14:882–8. [PubMed: 18622403]
85. Berger F, Lee YP, Luening AM, et al. Whole body skeletal imaging in mice utilizing microPET: optimization of reproducibility and applications in animal models of bone disease. Eur J Nucl Med Mol Imaging. 2002; 29:1225–36. [PubMed: 12418463]
86. Liao CP, Zhong C, Saribekyan G, et al. Mouse models of prostate adencarcinoma with the capacity to monitor spontaneous carcinogenesis by bioluminescence or fluorescence. Cancer Res. 2007; 67:7525–33. [PubMed: 17671224]
87. Hsieh CL, Xie Z, Yu J, et al. Non-invasive bioluminescent detection of prostate cancer growth and metastasis in a bigenic transgenic mouse model. Prostate. 2007; 67:685–91. [PubMed: 17342752]
88. Singh AS, Figg WD. In vivo models of prostate cancer metastasis to bone. J Urol. 2005; 174:820–6. [PubMed: 16093963]
89. Wirtzfeld LA, Wu G, Bygrave M, et al. A new three-dimensional ultrasound microimaging technology for preclinical studies using a transgenic prostate cancer mouse model. Cancer Res. 2005; 65:6337–45. [PubMed: 16024636]
90. Kasper S, Smith JA Jr. Genetically modified mice and their use in developing therapeutic strategies for prostate cancer. J Urol. 2004; 172:12–9. [PubMed: 15201729]
91. Narla G, DiFeo A, Fernandez Y, et al. KLF6-SV1 over-expression accelerates human and mouse prostate cancer progression and metastasis. J Clin Invest. 2008; 118:2711–21. [PubMed: 18596922]
92. Srikantan V, Valladares M, Rhim JS, et al. *HEPSIN* inhibits cell growth/invasion in prostate cancer cells. Cancer Res. 2002; 62:6812–6. [PubMed: 12460890]
93. Kelly KA, Setlur SR, Ross R, et al. Detection of early prostate cancer using a hepsin-targeted imaging agent. Cancer Res. 2008; 68:2286–91. [PubMed: 18381435]
94. Bisanz K, Yu J, Edlund M, et al. targeting ECM-integrin interaction with liposome-encapsulated small interfering RNAs inhibits the growth of human prostate cancer in a bone xenograft imaging model. Mol Ther. 2005; 12:634–43. [PubMed: 16039164]
95. Shi C, Zhu Y, Cerwinka WH, et al. Quantum dots: emerging applications in urologic oncology. Urol Oncol. 2008; 26:86–92. [PubMed: 18190836]
96. Gao X. Multifunctional quantum dots for cellular and molecular imaging. Conf IEEE Eng Med Biol Soc. 2007; 2007:524–5.

97. Gao X, Cui Y, Levenson RM, et al. In vivo targeting and imaging with semiconductor quantum dots. Nat Biotechnol. 2004; 22:969–76. [PubMed: 15258594]

98. Gao X, Chung LW, Nie S. Quantum dots for in vivo molecular and cellular imaging. Methods Mol Biol. 2007; 374:135–45. [PubMed: 17237536]