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Imaging techniques for prostate cancer: implications for focal therapy

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Abstract

The multifocal nature of prostate cancer has necessitated whole-gland therapy in the past; however, since the widespread use of PSA screening, patients frequently present with less-advanced disease. Many men with localized disease wish to avoid the adverse effects of whole-gland therapy; therefore, focal therapy for prostate cancer is being considered as a treatment option. For focal treatment to be viable, accurate imaging is required for diagnosis, staging, and monitoring of treatment. Developments in MRI and PET have brought more attention to prostate imaging and the possibility of improving the accuracy of focal therapy. In this Review, we discuss the advantages and disadvantages of conventional methods for imaging the prostate, new developments for targeted imaging, and the possible role of image-guided biopsy and therapy for localized prostate cancer.

Introduction

Prostate cancer is the most common noncutaneous malignancy affecting men in the US, with 186,320 new cases resulting in approximately 28,660 deaths in 2008.¹ Over the past two decades, prostate cancer diagnoses have become more common as a result of the aging population and the widespread use of screening tests (for example, serum PSA testing). While prostate-cancer-specific mortality has declined over the past 4 years, prostate cancer is the second leading cause of cancer-related deaths in men, with lung cancer being the most common, and colon cancer closely following prostate cancer.¹

The multifocal nature of prostate cancer has necessitated whole-gland therapy in the past; however, since the widespread use of PSA screening, patients are presenting with less-advanced disease. With earlier detection, and the knowledge that patients' outcomes are determined by the aggressiveness of one or more dominant lesions, focal therapy is now being considered as a treatment option. Focal therapy currently relies on imaging to locate the disease, but, despite advances in technology, prostate imaging of localized disease has several limitations that need to be overcome if focal therapy is to be developed further.

The role of imaging for prostate cancer can be divided into tumor localization, staging of disease, and the detection of recurrences. Herein, we will focus only on the first two topics. A critical challenge for imaging is to differentiate clinically significant disease from silent and indolent disease, a goal that has not yet been achieved. Ultimately, this determination

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will probably be made by tissue markers, but until the day arrives when we can reliably predict the biological behavior of prostate cancers, imaging will simply ‘point’ to the lesion without further specificity as to its aggressiveness. The aim of this article is to review the progress that has been made in prostate cancer imaging to date, and to discuss whether such imaging will be able to guide focal therapy in the future.

Current imaging modalities

TRUS

Transrectal ultrasonography (TRUS; Box 1) is the most commonly used modality for imaging the prostate gland. TRUS enables determination of prostate size and demonstration of the zonal anatomy, and prostate cancer lesions usually appear hypoechoic relative to normal tissue. TRUS has many advantages, including its portability, ease of use, lack of ionizing radiation, low cost, and its capability to perform real-time imaging. Ultimately, however, TRUS is not a high-resolution imaging modality. The inherent speckle pattern of ultrasonography limits the detection and definition of the margins of cancers. The capability of TRUS to delineate cancer foci is limited, and its sensitivity and specificity are low: small cancer foci are often not visible at all, and the majority of hypoechoic foci detected by TRUS are not malignant.² TRUS is also rarely useful in depicting extra-capsular extension of prostate cancer and seminal vesicle invasion, except when gross extension is present.

Box 1

Glossary terms for ultrasonography and CT

Ultrasonography

A technique in which high-frequency sound waves are bounced off internal organs, with the echo pattern converted into a two-dimensional image of the structures beneath the transducer. Transrectal ultrasonography uses an ultrasonography probe that is inserted into the rectum to create an image of the prostate.

Doppler ultrasonography

Ultrasonography that uses the Doppler effect—the change in frequency and wavelength of a wave for an observer moving relative to the source of the waves—to assess whether structures (usually blood) are moving towards or away from the ultrasonography probe, and their relative velocity.

Contrast-enhanced ultrasonography

A technique in which ultrasonography is performed after contrast agents are administered intravenously to the systemic circulation. The contrast agents contain gas-filled microbubbles; these microbubbles have a high degree of echogenicity, which is detected by ultrasonography.

CT

A technique that uses multiple two-dimensional X-ray images, taken around a single axis of rotation, to generate a three-dimensional image of the inside of an object. CT uses ionizing radiation.

The addition of color Doppler and/or power Doppler (Box 1) can increase the rate of tumor visualization by detecting regions of hypervascularity; however, the sensitivity of TRUS is not increased with Doppler because most small tumors are not angiogenic.³ Contrast-enhanced TRUS with microbubbles (Box 1) has been found to provide higher sensitivity for the detection of cancer foci than standard TRUS, and has increased the detection rate of

clinically significant prostate cancer in several studies.^{4–6} Furthermore, contrast-enhanced TRUS with microbubbles has been shown to detect prostate cancer in patients with previous negative biopsies but with persistently rising serum PSA values.⁷ The findings of contrast-enhanced TRUS can, however, be subtle, short-lived and similar to findings in patients with prostatitis. Additionally, contrast-enhanced TRUS with microbubbles for prostate cancer imaging is an off-label use, and has not been extensively tested. The advantages and disadvantages of ultrasonography techniques for prostate cancer imaging are summarized in Table 1.

CT

CT (Box 1) is a widely used modality in both the diagnosis and follow-up of nearly all malignancies, but it has only a limited role in the imaging of prostate cancer owing to its poor soft-tissue contrast resolution, which does not allow precise distinction of the internal or external anatomy of the prostate (Table 1). The major role of CT in patients with prostate cancer is for the detection of bony involvement and in nodal staging; however, CT only detects the enlargement of involved nodes, which is a late finding in patients with prostate cancer.

MRI

MRI (Box 2) allows anatomical and functional assessment of the prostate. MRI has better soft-tissue resolution than any other imaging method, which enables more-accurate lesion detection and local staging. The highest-resolution MRI for prostate imaging requires the combined use of an endorectal coil (Box 2) and a phased-array body coil (Box 2) on a magnet with a field strength of at least 1.5 Tesla, and preferably 3 Tesla; the higher the magnetic field, the higher the signal-to-noise ratio, and the better the image resolution and/or acquisition speed will be. Excellent results have also been achieved without an endorectal coil at high magnetic field strengths. Technical details of MRI of the prostate are available in a publication by Ocak *et al.*⁸

Box 2

Glossary terms for MRI and anatomical magnetic resonance techniques

MRI

This imaging modality uses a magnetic field to polarize protons within tissues. A pulse of energy is then directed into the tissue and knocks some of the protons out of alignment. When the pulse is turned off, radio waves can be detected as the protons move back into their aligned position.

Endorectal coil

A medical device placed into the rectum in order to obtain high-quality images of the organs within the pelvis, specifically the prostate gland. The endorectal coil consists of a probe with an inflatable balloon, which helps maintain appropriate positioning within the rectum.

Phased-array coil

This device consists of several independent coils connected in parallel or series, which help to receive magnetic resonance signals. It enables the acquisition of images with a large field of view and a high spatial resolution, as well as improved signal-to-noise ratio.

T1-weighted MRI

This technique measures how the protons realign relative to the external magnetic field. A 90° pulse is used to displace the protons. The protons are rotated into the X–Y plane, where they precess in phase. After the radiofrequency pulse is switched off, the protons come out of phase (dephase), and return to the Z-plane. The faster the protons realign (that is, shorter T1), the stronger the signal. Early measurement of this signal is required to differentiate between various tissues.

T2-weighted MRI

This technique measures how the protons realign relative to each other. A 90° pulse is used, and as the protons dephase, a 180° pulse puts them back in phase. In a T2 image, tissues that remain in phase for a long time and maintain a strong signal are emphasized (long T2). Delaying the sampling time after the 180° pulse enhances this effect.

Anatomical MRI—Anatomical MRI of the prostate includes T1-weighted (T1W; Box 2) and T2-weighted (T2W; Box 2) MRI sequences. On T1W images, the prostate gland appears homogenous with intermediate–low signal intensity, which makes differentiation of the zonal anatomy impossible. T1W images are important, however, because they can show the presence of hemorrhage secondary to a recent biopsy; hemorrhage is almost always hyperintense compared with normal parenchyma. T2W images are the ‘workhorse’ images for prostate cancer. Tissues with high water content are brighter than other tissues on T2W images; thus, the glandular peripheral zone appears high in signal, whereas the central stroma has lower signal intensity.

Tumors, which are characterized by the loss of the normal glandular pattern of acini and are separated by large amounts of water-poor desmoplastic reaction, are lower in signal intensity than normal peripheral zone glandular tissue. Peripheral zone cancers are usually round or ill-defined, and have low-signal-intensity foci. Various conditions, such as prostatitis, hemorrhage, atrophy, benign prostatic hyperplasia (BPH) and post-treatment changes can mimic cancer. Cancers in the central gland are even more challenging to detect than peripheral zone cancers, because the signal characteristics of the normal and hypertrophic central gland are usually similar to those of the tumor. Detecting prostate cancers in the background of hypertrophic transitional zones is especially problematic because of the heterogeneity of the background. In addition, hyperplastic transitional zones are characterized by cystic and fibrotic nodules that result in high and low signal respectively; the latter has the same appearance as that of cancers. In a retrospective study of 148 patients, Akin *et al.*⁹ defined the characteristics of transitional zone tumors, 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. These findings are inherently qualitative and subjective, and might be difficult to reproduce.

Extracapsular extension can be detected on T2W images by direct visualization of the extension of the tumor into the periprostatic fat. The secondary findings of extracapsular extension 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.¹⁰ The prostate capsule can usually be seen on T2W images, and any tumor that abuts the capsule and causes the capsule to lose its sharp margins should be considered suspicious for extracapsular extension (Figure 1).

On T2W images, seminal vesicle invasion appears as a region of focal low signal intensity within the normally high-signal seminal vesicles, and may arise by contiguous spread from a base lesion or without visible connection to the primary tumor. T2W MRI alone is reported to have ranges of sensitivity and specificity for cancer detection of 27–100% and 32–99%,

respectively; the sensitivity and specificity ranges for local staging and predicting the presence of extracapsular extension are 14.4–100% and 67–100%, respectively.^{11–23} Such large ranges reflect the different levels of experience, patient populations and diagnostic criteria used in the various studies.

Lymph node staging is more problematic than identifying extracapsular extension or seminal vesicle invasion with MRI. Diagnostic criteria for lymph node invasion traditionally depend on morphologic enlargement, although a form of contrast-enhanced MRI (Box 3), lymphotropic ultrasmall superparamagnetic iron oxide (USPIO)-enhanced T2*-weighted gradient-refocused echo MRI, has now been reported to be useful in the detection of small lymph node metastases.^{24,25} This contrast agent is available in parts of Europe, but the likelihood of it becoming available in the US is unclear because of regulatory hurdles.

Box 3

Glossary terms for functional magnetic resonance techniques

Dynamic contrast-enhanced MRI

A quantitative method of investigating microvascular structure and function by tracking the pharmacokinetics of injected low-molecular-weight contrast agents as they pass through the vasculature.

Two-compartment pharmacokinetic model

A method of analyzing dynamic contrast-enhanced MRI data by mathematically fitting the time–signal curve to permeability parameters reflecting flow from compartment 1 (the vascular space) to compartment 2 (the extravascular, extracellular space). The parameter K^{trans} reflects the forward leak of contrast media (compartment 1 to compartment 2) while the parameter k_{ep} reflects the reflux of contrast media from compartment 2 to compartment 1.

Magnetic resonance spectroscopy

A technique used to measure the levels of different metabolites in body tissues. The magnetic resonance signal produces a spectrum of resonances that correspond to different molecular arrangements.

Diffusion-weighted MRI

An MRI technique that measures the restricted diffusion of water in tissue.

Apparent diffusion coefficient

This method estimates the amount of water diffusion within MRI by varying the gradient field strengths and evaluating the amount of signal gain or loss. High apparent diffusion coefficient values indicate a large amount of water diffusion, whereas low apparent diffusion coefficient values indicate restricted diffusion, as occurs in tumors.

B field

This term refers to the additional magnetic field applied to images in order to measure the apparent diffusion coefficient.

Low-susceptibility liquids

Fluids used to avoid artifacts related to large differences in local magnetic fields within an image.

Magnetic resonance thermometry

A technique that uses the proton chemical shift detected using phase-difference MRI to measure temperature. Temperature maps of the target and surrounding tissues can be generated in almost real time.

Biopsy-related hemorrhage can cause artifacts on T2W scans that mimic cancer and thereby limit detection; however, as stated above, T1W MRI can be used to detect hemorrhage by high signal intensity; nonhemorrhagic cancers do not have high signal intensity on T1W MRI. Post-biopsy hemorrhage not only interferes with accurate evaluation of T2W images, but also confounds the results of the functional magnetic resonance methods of dynamic contrast-enhanced MRI (DCE-MRI) and magnetic resonance spectroscopy (MRS; Box 3). To ensure that TRUS-guided-biopsy-related hemorrhage does not interfere with MRI, the time interval between the biopsy procedure and MRI should be at least 8 weeks.²⁶ Even then, some cancers will continue to be obscured by hemorrhage. Though not applied routinely, MRI can be performed prior to TRUS-guided biopsy and to guide sampling of the prostate, specifically for tumors located in the anterior gland and/or central gland.

Functional MRI—Functional MRI modalities include DCE-MRI, MRS and diffusion-weighted MRI (DW-MRI; Box 3) (Figure 2). DCE-MRI evaluates the vascularity of tumors by providing quantitative kinetic parameters that reflect the flow of blood and the permeability of the vessels. Fast acquisition sequences, combined with rapid administration of a low-molecular-weight contrast agent, can be used to detect prostate cancer using a two-compartment pharmacokinetic model (Box 3). DCE-MRI increases the specificity of prostate MRI significantly compared with T2W scans alone.⁸ Tumors show early enhancement and early washout of the contrast agent, which enables tumor detection. When enhancement curves are mathematically fitted to two-compartment pharmacokinetic models, they produce permeability parameters, such as K^{trans} (wash in) and k_{ep} (wash out); the higher the tumor grade, the higher these parameters tend to be. A disadvantage of DCE-MRI is that small, low-grade tumors may not demonstrate abnormal enhancement on DCE-MRI.²⁷ Furthermore, abnormal enhancement patterns can also be seen in patients with BPH, which can make assessment of the central gland difficult.²⁸ However, in the glandular peripheral zone and anterior gland, DCE-MRI can be quite helpful in identifying lesions that are not suspected on T2W images.²⁹ Li *et al.*³⁰ demonstrated the association between prostate enhancement after USPIO particle administration and tumor grade in 60 patients with primary prostate cancer; the degree of enhancement (negative contrast in the case of USPIOs) correlated positively with tumor grade. DCE-MRI alone has reported sensitivity and specificity ranges of 46–96% and 74–96%, respectively, for detection of tumor lesions, but, as always, these ranges are highly dependent on patient selection, technique and diagnostic criteria.^{8,31–35} One concern regarding DCE-MRI is the possibility of inducing nephrogenic systemic fibrosis (a severe interstitial fibrosis that occurs after intravenous injection of gadolinium chelates) in patients with severe renal failure, especially those undergoing dialysis; therefore, the use of gadolinium-containing contrast agents should be carefully evaluated in such patients.

MRS is a modality that provides information about the cellular metabolites within the prostate gland; it displays the relative concentrations of key chemical constituents, such as citrate, choline and creatine. The normal prostate gland contains low levels of choline and high levels of citrate, whereas prostate cancers have increased levels of choline and decreased levels of citrate. Normal secretory epithelial cells of the prostate contain excess zinc, which inhibits the citrate-oxidizing enzyme aconitase, and high levels of citrate are produced. In prostate cancers, levels of zinc are lower, which leads to elevated aconitase activity and subsequently diminished amounts of citrate.³⁶ The high choline levels in prostate tumors are related to increased cell turnover and overexpression of choline kinase.³⁷ Thus, the ratio of choline to citrate is an index of malignancy.^{11,38} The majority of MRS

data in the current literature were obtained at 1.5 Tesla, where the ratio measured is really that of choline plus creatine to citrate (choline + creatine : citrate). Magnets with a magnetic flux density of 3 Tesla have also been employed in prostate MRS. Increased field strength leads to smaller voxel size (a three-dimensional volume element, analogous to the two-dimensional pixel), improved temporal resolution, and more-accurate separation of metabolite peaks. For instance, MRS performed at 3 Tesla enables distinction of the choline peak from the creatine peak, thereby improving specificity.³⁹ Besides analysis of choline, citrate and creatine content, newer image acquisition and analysis software may enable evaluation of other metabolites, such as polyamine peaks, which have also been associated with prostate cancers.⁴⁰ Integration of MRS into routine prostate MRI practice has improved tumor detection rates.^{41–43} Moreover, MRS has been used to help detect recurrence after therapy.^{44–46} Most observers agree, however, that MRS is technically challenging; it requires the assistance of onsite magnetic resonance physicists, and is not yet a ‘push-button’ technique. Its current use, therefore, is restricted to research settings.

DW-MRI, another functional magnetic resonance technique, evaluates the Brownian motion of free water in tissues. Tissue water diffusion is restricted in tumors because of increased cellularity and stroma. Prostate cancers often include tightly packed glandular elements with increased cellular density and diminished extracellular spaces, which can be detected as high-signal- intensity foci on raw DW-MRI, but are low in signal on apparent diffusion coefficient maps, which are summation images obtained from multiple ‘b field’ images (Box 3). Apparent diffusion coefficient maps reflect the amount of diffusion present; the lower the diffusion, the darker the lesion.^{47,48} With the emergence of high-field-strength magnets and the widespread use of endorectal coils filled with low-susceptibility liquids (Box 3) like perflubron, high-resolution DW-MRI can be routinely performed. Additionally, high b values (1,000–2,000 s/mm²) improve lesion detection.^{49–51} DW-MRI alone has wide ranges of sensitivity (57.0–93.3%) and specificity (57–100%).^{31,50,52–56} The advantages and disadvantages of the magnetic resonance techniques for imaging prostate cancer are provided in Table 2.

Radionuclide imaging

A variety of single photon and positron-emitting radionuclides have been used to image prostate cancer via radionuclide imaging (Box 4). These radionuclides have the advantages of improved specificity for cancer, but also have much lower resolution than TRUS, CT and MRI. The current role of radionuclide imaging for local prostate cancer is still evolving, but it is generally less widely used than MRI.

Box 4

Glossary terms for radionuclide imaging techniques

Radionuclide imaging

An imaging technique that introduces tiny amounts of radioactive material into a patient’s body, which is then detected by scanners or gamma camera systems.

Single photon emission computed tomography

A form of radionuclide imaging that uses radionuclides that emit a single photon. This method uses a gamma camera to acquire multiple two-dimensional images from multiple angles. Tomographic reconstruction is applied to yield a three-dimensional dataset; the final image shows the three-dimensional distribution of a radionuclide.

PET

A form of radionuclide imaging that uses positron-emitting radionuclides; the positrons annihilate electrons, which results in the production of two simultaneous and oppositely directed gamma rays. The tracer is introduced into the body using a biologically active molecule. Tomographic reconstruction is applied to yield a three-dimensional dataset.

Radiolabeled antibody imaging—Radiolabeled monoclonal antibodies directed towards specific cell-surface antigens have been extensively used in imaging and therapy of several cancer types. ^{111}In -capromab pendetide (ProstaScint®; Cytogen Corp, Princeton, NJ) is a radiolabeled murine monoclonal antibody directed towards an intracellular component of prostate-specific membrane antigen. Imaging with 5.0 mCi ^{111}In -capromab pendetide can be performed with planar or cross-sectional single photon emission CT (SPECT; Box 4). Images obtained several days after injection allow enough time for wash-out of the background signal. In theory, antibody imaging with ^{111}In -capromab pendetide allows for a specific molecular diagnosis of primary and secondary prostate cancer lesions.^{57–60} A limitation of ^{111}In -capromab pendetide imaging is that it is suboptimal for the detection of bone metastases, and is significantly less sensitive than bone scans in this regard.⁶¹ Furthermore, ^{111}In -capromab pendetide is not currently considered a promising agent for lesion detection within the prostate gland or for determining extracapsular extension, primarily because the internal target of ^{111}In -capromab pendetide requires that cell membranes be damaged before the antibody can bind. Excess unbound antibody leads to high background signal and poor spatial resolution, which can only partly be improved by coupling this technique with CT or MRI.⁶²

PET—PET (Box 4) is emerging as an important imaging tool. The images are obtained in three dimensions, and the intensity of the signal is proportional to the amount of tracer; therefore, the technique is potentially quantitative. While routine PET has limited spatial resolution (~4–6 mm), its resolution is better than that of SPECT. PET can also image specific physiological processes, such as the rate of glucose or fatty acid metabolism, which cannot be achieved with other imaging techniques.

The most common tracer for PET imaging, ^{18}F -fluoro-2-deoxy-2- β -D-glucose (^{18}F -FDG), is not effective in the diagnosis of localized prostate cancer. These tumors are not glucose dependent, and the tracer does not accumulate in the prostate. ^{18}F -FDG does, however, become more useful in patients with androgen-independent tumors.⁶³ Some localized prostate cancers are inexplicably highly glucose dependent and will be positive on ^{18}F -FDG PET scans obtained for reasons other than investigation for prostate cancer, although this finding is the exception rather than the norm. In several studies, remarkable similarities in the ^{18}F -FDG uptake in prostate tumors and BPH have been demonstrated. Additionally, intense bladder activity is usually present, which obscures the prostate and interferes with the identification of pelvic lymph node metastases.^{63–65} For these reasons, ^{18}F -FDG is not the ideal PET tracer for the initial staging and follow-up of prostate cancer. New radiotracers that target tumor proliferation, membrane turnover and amino acid transport are now under investigation.

Acetate is one such tracer that is being investigated. Acetate is a naturally occurring compound that is converted to acetyl-CoA, a substrate for the tri-carboxylic acid cycle that is incorporated into cholesterol and fatty acids. Acetate accumulates in tumors, although the exact mechanism of accumulation is unknown; one hypothesis is that acetate becomes incorporated into the membrane lipids of tumor cells.⁶⁶ Acetate is metabolized in various organs, and is excreted mostly via the pancreas, enabling imaging of the pelvis without confounding bladder activity; ^{11}C -acetate PET may, therefore, be able to detect prostate cancer and could potentially be used to monitor the effects of treatment. In four clinical

trials, ^{11}C -acetate PET was shown to be useful in the diagnosis, staging and restaging of prostate cancer.^{67–69} Although these few preliminary studies reveal promising results for ^{11}C -acetate PET, prospective clinical trials are needed to properly evaluate its role in localized disease. Moreover, the value of combining ^{11}C -acetate PET with MRI using a high field strength (3 Tesla) needs further exploration.⁷⁰ As prostate cancer is often a multifocal process, it is hoped that novel tracers like ^{11}C -acetate will eventually be used in conjunction with 3 Tesla MRI to identify tumor foci and guide local therapy.

As mentioned above, choline is an important component of the phospholipids in cell membranes, and elevated levels of choline and choline kinase have been detected in prostate cancer cells. Several choline analogs have been labeled with ^{11}C or ^{18}F for PET imaging; ^{11}C -choline has limited urinary excretion, and is thus well suited for prostate imaging. ^{11}C -choline PET has been shown to be useful in the diagnosis and staging of prostate cancer.^{71–73}

All ^{11}C -labeled compounds are limited by their short half-life (20 min). Longer-lived radioisotopes are now being used in the development of novel tracers, such as ^{18}F -fluorocholine (^{18}F -FCH), which has a half-life of 110 min and rapidly clears from the blood stream into the urine. Kwee *et al.*⁷⁴ evaluated ^{18}F -FCH PET in 15 patients with organ-confined prostate carcinoma who underwent radical prostatectomy, and detected tumors in 61 of 90 prostate sextants. In another study, Cimitan *et al.*⁷⁵ evaluated 100 patients with a PSA relapse; ^{18}F -FCH PET–CT identified recurrence in 53 patients.

Anti-1-amino-3- ^{18}F -fluorocyclobutane-1-carboxylic acid (anti- ^{18}F -FACBC) is a synthetic 3-leucine analog that is taken up by amino acid transporters, such as the L-type and the energy-dependent A-type transporters, into cancer cells. In initial studies, bladder excretion of anti- ^{18}F -FACBC was found to be low, and was observed 60 min after injection. Schuster *et al.*⁷⁶ used anti- ^{18}F -FACBC PET in a pilot study of 15 patients with recently diagnosed or recurrent prostate cancer, and correctly identified tumors in 40 of 48 prostate-cancer-containing sextants; moreover, recurrence was successfully detected in all four patients whose disease recurred.

16 β - ^{18}F -fluoro-5 α -dihydrotestosterone (^{18}F -FDHT), an androgen analog, is a radiotracer developed for evaluating androgen receptor expression *in vivo*. Initial studies performed by Larson *et al.*⁷⁷ included seven patients with clinically progressive metastatic prostate cancer who underwent ^{18}F -FDG and ^{18}F -FDHT PET scans, in addition to conventional imaging methods, such as bone scintigraphy, plain X-ray and CT. Conventional imaging identified 59 lesions, whereas ^{18}F -FDG and ^{18}F -FDHT were positive in 57 and 46 of these 59 lesions, respectively. Dehdashti *et al.*⁷⁸ used ^{18}F -FDHT PET in patients with advanced prostate cancer; this technique identified 12 out of 19 patients with cancer, and 24 out of 28 lesions. Additionally, ^{18}F -FDHT PET detected 17 meta-static lesions that were missed by conventional imaging. Follow-up ^{18}F -FDHT PET imaging after anti-androgen therapy demonstrated significantly reduced radiotracer uptake in all lesions. On the basis of these results, the lack of uptake of ^{18}F -FDHT is thought to indicate the presence of an androgen-resistant tumor; therefore, studies evaluating the utility of ^{18}F -FDHT PET for predicting androgen resistance are needed. Table 3 summarizes the advantages and disadvantages of the radionuclide imaging techniques.

Image-guided biopsy

In order to perform focal therapies for prostate cancer, direct biopsy needles and, ultimately, therapies that can be delivered into the areas identified as abnormal on imaging are required. Here, we discuss the current platforms available for image-guided biopsies.

TRUS-guided biopsy

TRUS-guided prostate biopsy is considered the gold standard modality for preoperative prostate cancer diagnosis, as it is a hand-held, real-time technique; however, owing to sampling errors, nearly 30% of cancers are missed at sextant biopsy. This figure is highly dependent on the patient population; for instance, low-risk patients tend to have smaller tumors that are harder to detect than tumors in high-risk patients. Moreover, sonographic imaging alone is not accurate for localizing or grading tumors.^{79,80} Improvements in TRUS-guided biopsy sensitivity and accuracy can be achieved by increasing the number of biopsies performed. At the extreme end of the spectrum, so-called 'saturation biopsies' are obtained from throughout the gland and their locations are carefully recorded. Over 100 biopsies can be obtained per patient during such procedures; however, owing to the inherent trauma to the prostate and the high cost of processing so many specimens, saturation biopsy is unlikely to be the diagnostic method of the future. Although TRUS by itself has limited sensitivity and specificity in the direct detection of prostate cancer, TRUS images combined with other types of imaging data could be suited to guiding biopsies and ablative therapies.

MRI-guided biopsy

MRI provides superior anatomical detail compared with CT and TRUS; hence, by combining tissue biopsy with this powerful imaging tool, a more-sensitive tissue sampling can be performed. Stereotactic placement of the needle under MRI guidance helps to target the suspected tumor site on MRI, and allows volumetric verification and documentation of the actual biopsy location, which can be used for future interventions.⁸¹ D'Amico *et al.*⁸² successfully performed the first MRI-guided prostate biopsy with an open magnet, using the transperineal approach, in a patient who had previously undergone proctocolectomy. Susil *et al.*⁸³ subsequently developed a transrectal system, which enabled precise MRI guidance, accurate targeting and intervention monitoring in a canine model. These authors demonstrated accurate placement of brachytherapy seeds under MRI guidance. Krieger *et al.*⁸⁴ have also reported the use of a novel, remotely actuated manipulator to access prostate tissue under an MRI-guidance device. This manipulator was designed for use in standard, high-field MRI scanners, which provide three-dimensional MRI-guided needle placement with millimeter accuracy; the authors demonstrated the feasibility of this system in both dogs and humans. Beyersdorff *et al.*⁸⁵ performed MRI-guided prostate biopsies in 12 patients in a closed 1.5 Tesla MRI unit. These investigators used a biopsy device that was compatible with magnetic resonance, consisting of a needle guide that could be visualized with MRI and manipulated mechanically from outside the magnetic resonance unit. They demonstrated that the device enabled MRI-guided core-needle biopsy of areas suspicious for cancer. Most recently, Susil *et al.*⁸⁶ demonstrated the accuracy and feasibility of a system that provides transrectal needle access to the prostate during direct imaging with a 1.5 Tesla MRI unit for placement of gold fiducial markers (a point of reference) and/or prostate biopsy.

MRI-guided prostate biopsy seems to be a promising method, especially in individuals with previous negative TRUS-guided biopsies. MRI-guided prostate biopsy not only enables direct visualization during diagnostic and therapeutic procedures, but can provide direct monitoring of temperature (for example, during magnetic resonance thermometry [Box 3]), to ensure adequate treatment.⁸⁷ The main disadvantage of MRI-guided biopsy is the magnetic environment, which makes interventional procedures complex, leading to prolonged occupancy of the magnetic resonance suite, increased costs, and patient discomfort because of procedural positioning. Another problem with MRI-guided biopsy is the need for motion correction during the biopsy procedure. In short, the magnetic resonance environment is less than ideal for conducting image-guided biopsies.

MRI-TRUS fusion-guided biopsy

Is it possible to combine the advantages of TRUS and MRI into one procedure? The sampling error of TRUS-guided biopsy can be compensated for by using MRI for prostate biopsies. Preprocedural MRI data are fused with real-time TRUS, thus combining the advantages of each modality. By using these complementary methods, the biopsy needle can be directed into suspicious regions identified previously on MRI, but under real-time TRUS guidance. Kaplan *et al.*⁸⁸ reported a technique used in two patients whereby high-resolution endorectal MRI detected suspicious areas of the prostate, which were then targeted using TRUS-guided biopsy. In previous studies, systems for fusing the preinterventional images (for example, CT and MRI) with real-time ultrasonography have been based on tracking an exterior localizer that assigns spatial coordinates to the ultrasonography probe, and then fuses these coordinates to the MRI system.^{89,90} Singh *et al.*⁹¹ demonstrated the utility of registration and fusion of real-time TRUS and preprocedurally acquired MRI for guiding prostate biopsies in five patients with prostate cancer. They used a TRUS transducer equipped with a commercial needle guide, and modified it with embedded sensors to enable spatial tracking and registration with MRI. This system was used for focal biopsy and fiducial marker placement without the need for an exterior localizer. The setup used in this study included an image registration and fusion system consisting of a custom visualization and registration workstation, interfacing with the Aurora® electromagnetic tracking system (Northern Digital Inc., Waterloo, ON, Canada). Endorectal biopsy guides were equipped with electromagnetic tracking sensors (Traxtal Inc., Toronto, ON, CA) compatible with the Aurora® system, which were attached to a front-fire endorectal ultrasonography probe (iU22 ultrasound system; Philips, Eindhoven, The Netherlands). Real-time transrectal ultrasonography images were transferred to the workstation using video frame-grabbing, enabling spatial localization of each ultrasonography frame with the tracking system (Figures 3 and 4).⁹²

Although the technique of combining images from real-time three-dimensional TRUS with those from three-dimensional MRI is preliminary, the resultant images can be used to direct biopsies and ultimately therapy. This technique does not require costly magnetic resonance room time for interventional procedures, and is a cheaper and faster procedure than MRI-guided prostatic procedures.

Image-guided focal treatment

Surgery and radiation therapy remain the standard treatments for localized prostate cancer, but because of their procedural morbidities and effects on quality of life, several less-invasive approaches have emerged as potential treatments for localized disease. Interest in these therapies is heightened because of the large number of young men who are being diagnosed with localized prostate cancer and who wish to avoid the long-term sequelae of radiation therapy and surgery. The less-invasive therapies include high-intensity focused ultrasonography, cryotherapy, radiofrequency ablation, brachytherapy, CyberKnife® (Accuray, Sunnyvale, CA) and photodynamic therapy.

High-intensity focused ultrasonography is a minimally invasive approach, in which a high-energy ultrasonography beam converges on a focal point, and is converted into thermal energy within the prostate producing local coagulative necrosis. Cryotherapy is a tissue ablation technique that employs liquid nitrogen to freeze and thaw tissue; for prostate lesions, this method can be applied under TRUS guidance, but the urethra and bladder must be protected from freezing and perforation with warming solutions.⁹³ Radiofrequency ablation leads to irreversible destruction of prostate tissue via thermal ablation within the cancerous tissue, which results in coagulative necrosis. This minimally invasive method has been shown to be safe, rapid, and well tolerated, and could be performed in an office

setting.⁹⁴ Brachytherapy seeds placed under the guidance of conventional imaging modalities (TRUS, CT, MRI or TRUS–MRI fusion) are another alternative for focal therapy. This method is considered safe and effective; however, acute genitourinary toxicity is a concern with high-dose-rate brachytherapy. Photodynamic therapy is a unique treatment wherein a systemic or locally administered photosensitizer is activated by light exposure, which has an ablative effect on the tissue. Photodynamic therapy is relatively new to the field of prostate cancer treatment and has only been tested in a limited number of patients.⁹⁵ Imaging guidance for radiotherapy has been evolving as a treatment approach for localized prostate cancer.^{96,97} Kupelian *et al.*⁹⁸ reported elimination of errors related to rectal distention by using CT during the initial planning stage of radiotherapy for localized prostate cancer.

Hopefully, these minimally invasive procedures will control prostate cancer without lowering a man's quality of life. Such methods are unlikely to be applicable to all men; those with microscopic disease will not be treated as their lesions are not visible on imaging, whereas focal therapies will be ineffective in those with advanced disease.

Conclusions

Prostate cancer is a common malignancy among men, and the current screening and imaging approaches aim to detect early-stage, organ-confined disease. Developments in imaging technologies, specifically MRI, have improved lesion detection and local staging; several PET tracers are under development which may further improve the accuracy of imaging. The evolution of these sophisticated imaging techniques into prostate interventions (biopsy and focal therapy) may allow accurate sampling and minimally invasive targeted treatments of localized prostate cancer.

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Learning objectives

Upon completion of this activity, participants should be able to:

1. Identify the benefits of transrectal ultrasound for the detection of prostate cancer.
2. Describe the features of prostate cancer on magnetic resonance imaging (MRI).
3. List the positron emission tomographic (PET) tracers useful in the detection of prostate cancer.
4. Describe the limitations of imaging-guided prostate biopsy.

Key points

- Since the widespread use of PSA screening, many patients present with localized prostate cancer, and focal therapy is now being considered for these patients
- Imaging currently has a major role in the staging of prostate cancer, but could also be used to direct focal therapy
- MRI is currently the most accurate imaging method for lesion detection and local staging
- Although experience is limited, PET with novel tracers may enable better lesion delineation and nodal staging than MRI
- Real-time transrectal ultrasonography and MRI fusion guidance can be performed at a lower cost and faster than real-time MRI-guided prostatic interventional procedures (biopsy and focal therapy)
- Integration of sophisticated imaging techniques into prostate interventions will allow accurate sampling and minimally invasive, targeted treatments for localized prostate cancer

Review criteria

Information for this Review article was obtained from the PubMed and Medline databases. The searches were performed by using a combination of the terms “prostate cancer”, “transrectal ultrasound guided biopsy”, “magnetic resonance imaging”, “PET imaging” and “focal therapy”. Full-text versions of the retrieved abstracts were obtained.

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Figure 1.

MRI of an 82-year-old man with prostate cancer and extracapsular extension. **a** | The axial T2-weighted image demonstrates a lesion (arrow) in the left mid anterior peripheral zone, with frank bulging secondary to extracapsular extension. **b** | The coronal T2-weighted image also shows the extracapsular extension (arrow). **c** | The lesion (arrow) is positive on an apparent diffusion coefficient map of diffusion-weighted MRI.

Figure 2. MRI of a 53-year-old man with prostate cancer. **a** | The axial T2-weighted image demonstrates a midline low-signal-intensity focus at the mid peripheral zone (arrow), indicating the prostate tumor. **b** | The sagittal T2-weighted image also demonstrates the midline low-signal-intensity focus (arrow). **c** | The lesion is positive on an apparent diffusion coefficient map (arrows). **d** | On the two-compartment pharmacokinetic model analysis of dynamic contrast-enhanced MRI, the K^{trans} and k_{ep} values of the tumor are high, which indicates a high likelihood of malignancy. **e** | On magnetic resonance spectroscopy, the choline-to-citrate ratio is increased, indicating malignancy.

Figure 3.

Work flow of MRI-TRUS fusion-guided prostate biopsy. MRI is performed before the biopsy. The images are segmented, and the target tumor is identified. The patient then undergoes 3D ultrasound acquisition, and the MRI and TRUS images are combined (registration). By use of real-time TRUS, and the corresponding MRI, the biopsy is targeted towards the tumor. Abbreviations: 3D, three-dimensional; DCE, dynamic contrast-enhanced MRI; DWI, diffusion-weighted MRI; MRS, magnetic resonance spectroscopy; T2W, T2-weighted MRI; TRUS, transrectal ultrasonography. Permission obtained from Sheng Xu and Jochen Kruecker, Philips Research North America, Briarcliff Manor, NY, 10510, USA.

Figure 4.

MRI of a 69-year-old man without previous documentation of prostate cancer. **a** | The axial T2-weighted image demonstrates a round-shaped, low-signal-intensity lesion at the right mid peripheral zone, which is suspicious for cancer (arrow). **b** | The sagittal T2-weighted image also shows the low-signal-intensity lesion (arrow). **c** | The apparent diffusion coefficient map of diffusion-weighted MRI is positive (arrow). **d** | The top two images are screen shots of the fused MRI-TRUS image guidance, illustrating the T2-weighted MRI fused with reference TRUS volume (color map). The bottom two images show the real-time TRUS and target information, corresponding to real-time TRUS at the time of needle deployment. The patient underwent a fused MRI-TRUS-guided biopsy, which was Gleason score 3 + 4 in 70% of the specimen. Permission obtained from Sheng Xu and Jochen Kruecker, Philips Research North America, Briarcliff Manor, NY 10510, USA. Abbreviation: TRUS, transrectal ultrasonography.

Table 1

Advantages and disadvantages of ultrasonography and CT for imaging prostate cancer

Type of imaging	Advantages	Disadvantages
TRUS	Enables determination of prostate size and demonstration of the zonal anatomy Portable Easy to use Lacks radiation Low cost Real-time imaging can be performed	Not a high-resolution imaging modality, and has an inherent speckle pattern Low sensitivity and specificity for prostate cancer Can rarely detect ECE and SVI
Doppler TRUS	Detects regions of hypervascularity	Most small tumors are not angiogenic
Contrast-enhanced TRUS with microbubbles	Higher sensitivity for cancer foci than standard TRUS	Findings are subtle, short lived, and can be similar to those in patients with prostatitis Prostate imaging is an off-label use
CT	Useful for detecting bony involvement and nodal staging of enlarged nodes	Has poor soft-tissue resolution, and is not a widely used modality for prostate cancer diagnosis or follow-up Uses ionizing radiation

Abbreviations: ECE, extracapsular extension; SVI, seminal vesicle invasion; TRUS, transrectal ultrasonography.

Table 2

Advantages and disadvantages of magnetic resonance techniques for imaging prostate cancer

Type of imaging	Advantages	Disadvantages
MRI	Allows anatomical and functional imaging of the prostate MRI is more accurate than any other current imaging modality for lesion detection and staging	Expensive Not ideal for real-time imaging
T1W MRI	Detects hemorrhage secondary to prostate biopsy as hyperintense regions	Prostate gland appears homogeneous
T2W MRI	Differentiates zonal anatomy Cancers are low in signal Glandular peripheral zone tumors appear as round or ill-defined low-intensity foci ECE can be directly observed, and numerous secondary findings can indicate ECE SVI appears as focal low-signal intensity within the normally high signal seminal vesicles	Prostatitis, hemorrhage, atrophy, BPH and post-treatment changes can mimic cancer Central-gland tumors have similar signal characteristics to the normal and hypertrophic central gland Hyperplastic transitional zones with cystic and fibrotic nodules can have the same signal pattern as that of cancers Lymph node staging is difficult and relies on morphologic enlargement of nodes
DCE-MRI	Detects vascularity Increased specificity compared with T2W MRI alone; tumors show early enhancement and early washout of the contrast agent	Small, low-grade tumors may not demonstrate abnormal enhancement Patients with BPH can have abnormal enhancement patterns that are similar to those of patients with central-gland tumors Possibility of inducing nephrogenic systemic fibrosis with gadolinium-based contrast agents in patients with severe renal failure
MRS	Provides concentrations of citrate, choline and creatine; high levels of choline and low levels of citrate can indicate cancer	Technically challenging and requires onsite magnetic resonance physicists
DW-MRI	Prostate cancers appear as high-intensity foci, and low in signal on ADC maps	Findings can be nonspecific because hyperplastic changes can also show low diffusion

Abbreviations: ADC, apparent diffusion coefficient; BPH, benign prostatic hyperplasia; DCE-MRI, dynamic contrast-enhanced MRI; DW-MRI, diffusion-weighted MRI; ECE, extracapsular extension; MRS, magnetic resonance spectroscopy; SVI, seminal vesicle invasion; T1W, T1-weighted; T2W, T2-weighted.

Table 3

Advantages and disadvantages of radionuclide imaging for imaging prostate cancer

Type of imaging	Advantages	Disadvantages
Radiolabeled antibody imaging with ^{111}In -capromab pendetide	Allows a specific diagnosis of primary or secondary prostate cancer lesions	Suboptimal for bone metastases detection Requires cell membranes to be damaged for the antibody to bind Cell membrane damage causes poor spatial resolution and high background signal
PET	High sensitivity and requires only a small amount of radioactive compound Signal is proportional to tracer, so could be quantitative Can image physiological processes	Limited spatial resolution
^{18}F -FDG PET	Sometimes detects inexplicably highly glucose-dependent prostate cancer	Not effective for imaging most prostate cancers Intense bladder activity obscures the prostate
^{11}C -acetate PET	Accumulates in the prostate Limited bladder excretion minimizes obscuring of prostate	Short half-life
^{11}C -choline PET	Limited bladder excretion minimizes obscuring of prostate	Short half-life
^{18}F -FCH PET	Half-life of 110 min and rapidly clears from blood into urine	Only preliminary results available
Anti- ^{18}F -FACBC PET	Limited bladder excretion minimizes obscuring of prostate Long half-life High sensitivity for cancer and recurrence	Only preliminary results available
^{18}F -FDHT PET	Lack of uptake could indicate an androgen-resistant tumor Long half-life	Only preliminary results available

Abbreviations: Anti- ^{18}F -FACBC, anti-1-amino-3- ^{18}F -fluorocyclobutane-1-carboxylic acid; ^{18}F -FCH, ^{18}F -fluorocholine; ^{18}F -FDG, ^{18}F -fluoro-2-deoxy-2-D-glucose; ^{18}F -FDHT, 16 β - ^{18}F -fluoro-5 α -dihydrotestosterone.