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Imaging of prostate cancer

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Purpose of review

Appropriate imaging of prostate cancer is a crucial component of staging and therapy application. The purpose of this review is to highlight the most important developments in novel imaging modalities reported in the past year.

Recent findings

Transrectal ultrasound is used to guide needle biopsy and brachytherapy. Improved results are obtained with color and power Doppler transrectal ultrasound with sonographic contrast agents. The role of elastography in prostate cancer remains to be elucidated. Magnetic resonance imaging is now widely used for staging before treatment and accumulating data indicate the utility of this technique with magnetic resonance spectroscopy in staging and follow-up. Positron-emission tomography alone or in combination with CT imaging with the new radiotracers ^{11}C-choline, ^{18}F-fluorocholine, ^{11}C-acetate and ^{18}F-fluoride have shown promising results. Further investigations in larger clinical studies are necessary to establish the role of these imaging techniques in the management of patients with prostate cancer.

Summary

This report provides a summary of novel types of imaging and indicates their promise in prostate cancer.

Keywords

elastography, magnetic resonance imaging, magnetic resonance spectroscopy, positron emission tomography, prostate cancer, transrectal ultrasonography

Curr Opin Oncol 19:000–000. © 2007 Lippincott Williams & Wilkins.

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Current Opinion in Oncology 2007, 19:000–000

Abbreviations

FDHT	fluoro-5-α-dihydrotestosterone
MRS	magnetic resonance spectroscopy
PSA	prostate specific antigen
ROC	receiver operating characteristic
SUV	standardized uptake value
SVI	seminal vesicle invasion
TRUS	transrectal ultrasound

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Introduction

The increased awareness of prostate cancer as a major cause of male cancer mortality has generated a new challenge for imaging of this disease. Primary or recurrent prostate cancer can be curatively treated when it is confined to the prostate. In these patients the therapy of choice is radical prostatectomy. If tumor has spread beyond the gland, chemotherapy, immunotherapy, or hormonal therapies are currently used. Metastatic prostate cancer, however, cannot be cured with these treatment modalities. Thus, it is important, at primary diagnosis, follow-up and recurrence, to obtain accurate assessment of the disease stage in order to decide the most effective treatment strategy. Conventional imaging techniques are limited in initial staging of the tumor, quantification of the tumor volume and its location inside the prostate, in follow-up of treatment and early identification of recurrence. Traditional morphologically based prostate imaging is now being complemented by functional and molecular imaging techniques for prostate cancer. The purpose of this review is to highlight the most important developments that have been published in the past year.

Transrectal ultrasonography

Transrectal ultrasonography (TRUS) is widely used to guide needle biopsy and brachytherapy. Color and power Doppler use reflected sound waves to evaluate blood flow through local vessels. Higher blood flow is often associated with areas of malignancy. Thus, these techniques may help to guide biopsy of the prostate.

Contrast enhancement

Using intravenous microbubble agents in combination with color and power Doppler imaging modalities, an increase in signal is obtained in areas of increased vascularity. In a study conducted by Pelzer *et al.* [1], 380 patients were suspected of having prostate cancer with a prostate specific antigen (PSA) level between 4 and 10 ng/ml contrast. Enhanced color Doppler targeted biopsies (five cores) in areas of hypervascularity were compared with standard biopsies (10 cores). Based on cancer detected by biopsy the detection rate of targeted biopsy cores was significantly better than standard biopsy cores (32.6% versus 17.9%, $P < 0.01$) Similar results were found in a two other studies. Halpern *et al.* [2] showed that contrast enhanced sonography targeted cores improved the detection rate of prostate cancer in 301 patients compared with sextant cores. With respect to the characterization of tissue as benign versus malign, intermittent harmonic

imaging was more effective than grey scale and Doppler imaging. The other study by Yi *et al.* [3•] evaluated the usefulness of contrast enhanced sonography in 48 patients with an indeterminate PSA level (4–10 ng/ml) and negative findings on digital exploration. Sensitivity on biopsy site was greater on contrast enhanced sonography (68%) than on grey scale (39%) and color Doppler (41%) sonography. Drudi *et al.* [4] showed that contrast enhanced sonography may also be used in the diagnosis of local recurrence after radical prostatectomy in patients with increasing PSA.

Elastography

Elastography is an imaging technique that evaluates the elasticity of the tissue. Miyanaga *et al.* [5] investigated 29 patients with untreated prostate cancer. The sensitivity of elastography, TRUS and digital rectal examination were 93%, 59% and 55%, respectively. Elastography may be used for biopsy guidance of prostate cancer. In a study by Konig *et al.* [6], elastography detected 84% of the 151 true positive cancer patients in a group of 404 investigated patients with suspected prostate cancer. Curiel *et al.* [7] used elastography for monitoring high-intensity focused ultrasound treatment in 20 prostate cancer patients. The results indicated a role in monitoring treatment response, but the elastographic measurements underestimated the volume compared with the volume measured with MRI. Although the results with elastography had shown some promising results, its role in prostate cancer needs to be evaluated further.

Magnetic resonance imaging and magnetic resonance spectroscopy

MRI, magnetic resonance spectroscopy (MRS) and PET are differently based molecular approaches. MRI detects the nuclear magnetic resonance spectra of water in tissues and reflects gross internal anatomy, whereas MRS detects the resonance spectra of chemical compounds other than water, reflecting in-situ chemistry. The difference between MRS and radiolabeled studies is that the same type of magnetic nucleus (e.g. ^{1}H) permits different compounds of biochemical interest to be distinguished, whereas a single radionuclide (e.g. ^{18}F, ^{11}C) can only identify a single compound.

Tumor localization and staging

One may assume that a combination of both methods, MRI and MRS, could improve diagnostic results because the morphological/anatomical base given by MRI is an important aid to localize biochemical findings by MRS acquired in the same examination in a coregistered way. The different technical modalities (e.g. MRI with an endorectal, pelvic or combined coil, dynamic contrast enhanced, magnetic field strength), and different patient groups, however, may lead to results that can only be compared in a limited way to point out the present trends. Wetter *et al.* [8] evaluated combined MRI and MRS of the prostate for staging accuracy in 50 patients with prostate carcinoma. The potential of MRS to differentiate between T2 and T3 tumors was compared with MRI. The mean tumor volumes, estimated by MRS, differed significantly between T2 and T3 tumors. The descriptive parameters of MRI and MRS did not differ significantly; sensitivity and specificity were 75% and 87%, respectively, for MRI and 88% and 70%, respectively, for MRS. Improvement in staging performance was found by combining MRI with MRS at 3.88-voxel threshold (sensitivity 75%, specificity 93%), but the difference for MRI alone was not statistically significant.

Futterer *et al.* [9••] prospectively evaluated the accuracy of T2-weighted MRI, dynamic contrast-enhanced MRI imaging, and quantitative three-dimensional proton MRS imaging of the entire prostate for prostate cancer localization, with whole-mount histopathology section findings as the reference standard. Thirty-four consecutive men with a mean PSA of 8 ng/ml were examined. The accuracy in tumor localization with dynamic contrast-enhanced MRI was significantly better than that with three-dimensional MRS imaging ($P < 0.01$). Compared with use of T2-weighted MRI alone, use of both dynamic contrast-enhanced MRI and three-dimensional MRS imaging significantly improved accuracy in prostate cancer localization.

Therapy planning, follow-up and restaging

Following advances in conformal radiotherapy, target definition is now an important issue. While MRI and CT provide images of excellent spatial resolution, they do not always provide sufficient contrast to identify tumor extent or to identify regions of high cellular activity that may be targeted with boost doses. Identification of differently aggressive areas of a biologically inhomogeneous tumor mass can be important for individual therapy planning and follow-up. It could be applied for more appropriately targeting using intensity modulated radiotherapy. Thus, a biological, inhomogeneous dose distribution can be generated, the so-called dose painting. MRS is an alternative approach that holds great promise for aiding target definition for radiotherapy treatment planning, and for evaluation of response and recurrence. There is only limited new information, however, with respect to new clinical studies.

External-beam radiation therapy

Pucar *et al.* [10] carried out a prospective evaluation of the correlation between MRI and MRS with pathologic findings after external-beam radiation therapy. Sextant biopsy, digital rectal examination, MRI, MRS, and salvage radical prostatectomy with step-section pathologic examination were performed in nine patients with increasing PSA levels after external-beam radiation therapy. Sensitivity and

specificity of sextant biopsy, digital rectal examination, MRI, and MRS were determined by using a prostate sextant as the unit of analysis. MRI and MRS showed estimated sensitivities of 68% and 77%, respectively, while sensitivities of biopsy and digital rectal examination were 48% and 16%, respectively. MRS appeared to be less specific (78%) than the other three tests, each of which had specificity higher than 90%.

Brachytherapy

Follow-up MRI after brachytherapy, when recurrence is suspected, is difficult because of radiation-induced changes. Furthermore, susceptibility artefacts from radioactive seeds in the peripheral zone compromise MRS. Barnes *et al.* [11] reported a case in which combined MRI/MRS was useful for the detection of prostate cancer in the transitional zone in patients previously treated with magnetic resonance-guided brachytherapy. The authors proposed that MRI/MRS may help to detect recurrent prostate cancer, guide prostate biopsy, and help manage salvage treatment decisions.

Prospective value (MRI and Kattan n omogram)

Preoperative identification of seminal vesicle invasion (SVI) is an important factor for staging and prognosis and may modify treatment selection and treatment planning. The Kattan nomograms generally use a combination of three factors (e.g. PSA, Gleason score, clinical stage) to determine the probability of PSA relapse after local therapy. Wang *et al.* [12••] studied the value of adding endorectal MRI to the Kattan nomograms for predicting SVI. They investigated 573 patients who underwent MRI before prostate cancer surgery. MRI findings, individual clinical variable PSA level, Gleason grade, clinical stage, greatest percentage of cancer in all biopsy cores, percentage of positive cores in all biopsy cores, and perineural invasion, and the Kattan nomograms were evaluated with respect to SVI prediction; surgical pathologic analysis was used as the reference standard. At pathologic analysis, 28 (4.9%) of 573 patients had SVI. Endorectal MRI (0.76) had a larger area under the receiver operative characteristic (ROC) curve than any clinical variable (0.62–0.73). At multivariate analysis, MRI results, Gleason grade, PSA level, and the percentage of cancer in all biopsy cores were significantly associated with SVI ($P \leq 0.02$). The Kattan nomograms plus MRI (0.87) had a significantly larger ($P < 0.05$) area under the ROC curve than either MRI alone (0.76) or the Kattan nomograms alone (0.80). The authors concluded that the addition of MRI contributes significant value to the Kattan nomograms for predicting SVI.

Positron-emission tomography

PET scans use pharmaceuticals containing radionuclides that decay by the release of positrons to produce whole-body tomographic images. PET can be combined with CT (PET/CT) to produce high-resolution images. In prostate cancer, the use of ^{18}F-fluorodeoxyglucose (FDG) PET has been limited compared with other cancers because urinary excretion of ^{18}F-FDG may mask pathological uptake. Furthermore, prostate tumors often have low metabolic glucose activity and vary widely in their rate of growth, aggressiveness, and tendency to metastasize. New and more favourable PET tracers based on metabolism different from glucose, however, have now been investigated. These are ^{11}C or ^{18}F-choline and ^{11}C-acetate, which are related to membrane lipid metabolism, or ^{11}C-methionine and 18F-fluoro-L-thyrosine, being related to protein turnover. Imaging of ^{18}F-fluoride turnover in prostate cancer bone metastases is another new approach. Based on such metabolic and hormone-related tracers [e.g. ^{18}F-fluoro-5α-dihydrotestosterone (FDHT)], including multimodal imaging and sensitivity improvements in PET/CT scanning techniques, diagnosis and staging of prostate cancers by PET and PET/CT has rapidly expanded in recent years.

^{11}C-choline PET

The value of ^{11}C-choline PET in 58 patients with suspected prostate cancer was investigated by Scher *et al.* [13••]. The prevalence of prostate cancer in the patients included was 63.8%. ^{11}C-PET and PET/CT showed a sensitivity of 86.5% and a specificity of 61.9%. In a ROC calculation in order to achieve the same sensitivity for direct comparison, the authors calculated a standardized uptake value (SUV) maximum cut-off value of 3.3 to differentiate between benign and malignant processes, which resulted in a sensitivity of 70.3% with a specificity of 57.1% in the detection of primary cancer. In comparison, the calculation for 70.3% sensitivity in PSA ended in a cut-off value of 7.2 ng/ml and a lower specificity of 52.4%. Concerning metastatic disease, ^{11}C-choline PET showed a sensitivity of 81.8%.

Similar results were found in a study by Reske *et al.* [14••]. In 26 patients with prostate cancer ^{11}C-choline PET was able to detect and locate major areas with carcinoma and differentiate cancer segments from those with benign lesions or normal prostate tissue. The sensitivity was 81% and the specificity 87%. The maximal ^{11}C-choline SUV did not correlate significantly with PSA or Gleason score but did correlate with T stage. From a clinical perspective, ^{11}C-choline PET/CT may be used for stereotactic tissue sampling in patients with clinical suspicion of prostate cancer and negative core biopsies. Farsad *et al.* [15] reported a similar approach in part of their study. In three of 36 patients, the initial prostate core biopsies failed to detect prostate cancer. ^{11}C-choline PET/CT-guided rebiopsy revealed prostate cancer in these patients. In the same study the sensitivity and specificity of ^{11}C-choline PET/CT for detection and

localization of prostate cancer within the prostate were 66% and 81%, respectively.

In a study of 43 patients with known prostate cancer (mean PSA of 12 ng/ml), Martorana *et al.* [16•] assessed the sensitivity of ^{11}C-choline PET/CT for intraprostatic localization of primary cancer, and compared its performance with TRUS-guided biopsy. ^{11}C-choline PET/CT had 83% sensitivity for intraprostatic localization of primary prostate cancer nodules 5 mm or greater. For extraprostatic extension, sensitivity of ^{11}C-choline PET/CT was low in comparison with MRI (*22%* versus 63%, $P < 0.001$).

Yamaguchi *et al.* [17] compared ^{11}C-choline PET with MRI and MRS in 20 patients with early stage prostate cancer. Interestingly, the study showed a diagnostic sensitivity of ^{11}C-choline PET of 100% for primary lesions, while the sensitivities of MRI and MRS were only 60% and 65%, respectively. No significant correlation between SUVmax and Gleason score or tumor grade were found.

^{18}F-fluorocholine PET

Kwee *et al.* [18••] compared ^{18}F-fluorocholine uptake in malignant and benign areas of the prostate in 26 patients with prostate cancer at two time points to determine the suitability of delayed or dual-phase ^{18}F-fluorocholine PET for localizing malignancy in the prostate gland. The mean SUVmax for dominant malignant regions increased significantly between initial and delayed scans while the mean SUVmax for probable benign regions decreased significantly between the two scans. The study indicated that delayed or dual-phase ^{18}F-fluorocholine PET may improve the imaging of malignant areas of the prostate.

Accurate staging with detection of lymph node metastases in prostate cancer has important implications for prognosis and treatment. Häcker *et al.* [19] investigated whether preoperative ^{18}F-fluorocholine PET/CT could detect lymph node metastases in 20 patients with prostate cancer. ^{18}F-fluorocholine PET/CT was not useful for detecting locoregional lymph node metastases in this study. Schmid *et al.* [20] obtained conflicting results in a study with 19 prostate cancer patients. Results from the study showed that ^{18}F-fluorocholine PET/CT may be promising for detecting local recurrence and lymph node metastases. Both studies were small and the role of ^{18}F-fluorocholine PET/CT for detecting lymph node metastases remains to be elucidated.

In a study by Cimitan *et al.* [21••] 100 patients with prostate cancer with a persistent increase in PSA after radical prostatectomy ($n = 58$), radiotherapy ($n = 21$) or hormonal therapy alone ($n = 21$) were investigated. Of the 100 patients, 54 had positive ^{18}F-fluorocholine PET/CT scans. Malignant disease was confirmed in all but one. Almost all negative ^{18}F-PET/CT scans (41/46) were observed in patients with PSA lower than 4 ng/ml and most true positive PET/CT scans (43/53) were observed when PSA was higher than 4 ng/ml. The authors conclude that ^{18}F-fluorocholine PET/CT is not likely to have an impact in the management of prostate cancer patients with biochemical recurrence until PSA increases to above 4 ng/ml. Conflicting results were found by Heinisch *et al.* [22•] in a smaller study with 34 patients with increasing PSA after radical prostatectomy ($n = 31$) and radiotherapy ($n = 3$). ^{18}F-fluorocholine PET/CT were able to yield true positive findings even at PSA lower than 5 ng/ml. In the study by Schmid *et al.* [20], ^{18}F-fluorocholine PET was also able to detect tumors in 19 patients with PSA lower than 5 ng/ml.

^{11}C-acetate PET

Three new studies investigated the diagnostic potential of ^{11}C-acetate PET in the early detection of prostate cancer recurrence. In the study by Albrect *et al.* [23], 32 prostate cancer patients were included with increasing PSA after initial radiotherapy ($n = 17$) or radical surgery ($n = 15$). The study showed that ^{11}C-acetate PET may be valuable in the early evaluation of prostate cancer relapse. Similar results were found in the study by Sandblom *et al.* [24]. In the study, 20 patients with increasing PSA after radical prostatectomy were included. Uptake was seen in patients with PSA levels as low as 0.5 ng/ml. Pathological uptake was seen in 75% of the patients. In this study, however, false positive uptake was seen in three of the patients. The study by Wachter *et al.* [25] also used ^{11}C-acetate PET in patients with increasing PSA after initial therapy, which was helpful in the following management of some patients.

^{18}F-fluoride PET and bone metastases

Currently radionuclide bone scans are the gold standard for detecting bony metastasis secondary to prostate cancer. Bone scintigraphy of the entire body using technetium-99 m methylene diphosphonate (^{99m}Tc MDP) is the most widely applied method. The PSA level at which to recommend a bone scan after treatment of early prostate cancer is controversial, however. Warren *et al.* [26••] correlated the incidence of positive bone scans with PSA in 8.113 men with localized prostate cancer who were followed in the Early Prostate Cancer Trial. The authors concluded that bone scans can be confidently eliminated in the follow-up of patients with early prostate cancer after standard treatment of those with PSA levels less than 5 ng/ml. This level can be increased to 20 ng/ml with caution in those patients treated with watchful waiting. The study by Salonia *et al.* [27] confirmed that bone metastases are more frequent in patients with high PSA and poorly differentiated tumors regardless of the patient's age. In a prospective study by Even-Sapir *et al.* [28••], bone scan and ^{18}F-fluoride PET/CT were

performed on the same day in 44 patients with high-risk prostate cancer. The authors reported that ^{18}F-fluoride PET/CT for detection of bone metastases in patients with high-risk prostate cancer was more specific than ^{18}F-fluoride PET alone and more sensitive and specific than planar and single photo emission computed tomography (SPECT) bone scintigraphy. Similar findings were shown in a case report by Gutman *et al.* [29].

^{11}C-methionine PET and receptor imaging with ^{18}F-FDHT PET

Tóth *et al.* [30] used ^{11}C-methionine PET in a study of 20 patients with increased PSA (mean PSA 9.36 ng/ml) and negative repeated biopsies. ^{11}C-methionine PET was positive in 75% of the patients. Dehdashti *et al.* [31] investigated the feasibility of the androgen receptor imaging with ^{18}F-FDHT by PET [31]. Only patients ($n = 20$) with advanced prostate cancer (mean PSA of 86.9 ng/ml) were included in the study. ^{18}F-FDHT PET was positive in 63% of the patients. The androgen receptor content of the prostate cancer lesions was not investigated.

Conclusion

Several advances in the imaging of prostate cancer have been made during the past year. Color and contrast-enhanced targeted biopsy alone or addition of these techniques to systematic biopsies improves the detection of prostate cancer. The role of elastography in prostate cancer still needs further investigation. MRI has the ability to improve accuracy in staging of localized prostate cancer and MRS may improve the accuracy of MRI tumor localization. PET and PET/CT imaging with the new radiotracers ^{11}C-choline, ^{18}F-fluorocholine and ^{11}C-acetate have shown promising results. Investigations in larger clinical studies are necessary, however, to establish the single and combined role of MRI, MRS and PET/CT. Additional refinements and techniques are expected to further improve the performance of these new imaging modalities in the management of prostate cancer.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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