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# Imaging in Prostate Cancer Staging: Present Role and Future Perspectives

## Key Words

Prostate cancer · Staging · MRI · Diffusion-weighted MRI · Dynamic contrast-enhanced MRI · Magnetic resonance spectroscopy · Prostate ultrasonography imaging · Positron emission tomography

## Abstract

Despite recent improvements in detection and treatment, prostate cancer continues to be the most common malignancy and the second leading cause of cancer-related mortality. Thus, although survival rate continues to improve, prostate cancer remains a compelling medical health problem. The major goal of prostate cancer imaging in the next decade will be more accurate disease characterization through the synthesis of anatomic, functional, and molecular imaging information in order to plan the most appropriate therapeutic strategy. No consensus exists regarding the use of imaging for evaluating primary prostate cancer. However, conventional and functional imaging are expanding their role in detection and local staging and, moreover, functional imaging is becoming of great importance in oncologic management and monitoring of therapy response. This review presents a multidisciplinary perspective on the role of conventional and functional imaging methods in prostate cancer staging.

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## Introduction

Prostate cancer is the most common malignancy in the European Union and the second among men in the United States being the second leading cause of cancer-related deaths [1, 2]. The face of prostate cancer is changing: its incidence is increasing as routine screening [e.g. serum prostate-specific antigen (PSA) and digital rectal examination (DRE)] becomes more common; on the other hand, the widespread use of screening tests has led to a significant decrease in prostate cancer-related mortality, likely due to earlier detection [3]. Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program demonstrate a remarkable decrease in the percentage of patients with distant metastatic disease at the time of diagnosis, from 20% for the period 1974–1985 to 5% for the period 1995–2000 [4–6]. Earlier detection of prostate cancer has brought new challenges to clinical assessment and treatment strategies – challenges that are compounded by the variability in natural history of the disease within the population at risk.

The thrust of cancer care in the new millennium is a risk-adjusted patient-specific therapy designed to maximize cancer control while minimizing the risks of complications. Prostate cancer requires accurate character-

ization and selection of the optimal therapeutic approach from a bewildering array of alternatives: active surveillance, hormonal treatment, radiation therapy and surgery. Recent focal ablative therapies such as cryoablation, radiofrequency ablation, and high intensity-frequency ultrasound have been added to the list of options [7].

Imaging is becoming increasingly important in the assessment of prostate cancer because it can guide treatment selection, as well as treatment planning. The literature is replete with controversy about the value of imaging, ranging from enthusiastic endorsement to serious skepticism. Data from the Cancer of the Prostate Strategic Urologic Research Endeavor show that from 1995 to 2002, there was a national shift toward fewer imaging studies in all risk categories; the proportion of patients receiving any staging imaging test decreased by 63% in low-risk patients, by 25.9% in intermediate-risk patients, and by 11.4% in high-risk patients [8]. The most precipitous decreases occurred in bone scan utilization rates, which decreased by 68.2, 24.6 and 11.1% in the low-, intermediate-, and high-risk groups, respectively. To some degree, these changes reflect the more appropriate use of imaging in response to the downward stage migration caused by PSA screening, but it is clear that some high-risk patients are proceeding to treatment without appropriate imaging evaluation [8]. Optimal use of imaging is not easy to define. Different imaging modalities result more appropriate in different disease stages and for the definition of the proper therapeutic option [9].

The menu of available imaging options is continuously evolving in response to changes in clinical care, scientific discoveries, and technologic innovations. Transrectal US, MRI, CT, radionuclide bone scanning, and positron emission tomography (PET) each have advantages, disadvantages and specific indications [10–12]. This review will provide a multidisciplinary perspective of current trends in imaging technique for staging prostate cancer.

### Evidence Acquisition

The authors searched the Medline, Embase, and Cochrane Library databases. Only English-language studies were evaluated. The last search was performed in May 2011.

### Local Disease

#### *Transrectal Ultrasound*

Transrectal ultrasound (TRUS) is the most widely used modality for imaging prostate gland and is mainly used to guide prostate biopsies. This imaging modality has been used for local staging of prostate cancer in some of the past studies but is generally considered insufficient [13]; its ability to delineate cancer foci is limited, with sensitivity and specificity varying at around 40–50% [9] and is also rarely useful in local staging because extracapsular extension (ECE) and seminal vesicles invasion (SVI) are challenging to visualize except when gross extension is present [9, 14]. The criteria for identifying ECE on TRUS are bulging and/or irregularity of the capsule adjacent to a hypoechoic lesion; the length of the contact of a visible lesion with the capsule is also associated with the probability of ECE [13]. SVI is heralded by a visible extension of a hypoechoic lesion at the base of the prostate into a seminal vesicle or by echogenic cancer within the normally fluid-filled seminal vesicle [15]; asymmetry of the seminal vesicles or solid hypoechoic masses within the seminal vesicles are indirect signs of disease extension [15].

Authors of studies performed in the 1980s, when cancers tended to be more advanced (stage T3) and more readily palpated, reported sensitivity in the range of 80% for detecting ECE and SVI at transrectal US [16]. Accuracy improved when US findings were interpreted in concert with DRE findings and PSA level to estimate the likelihood of extraprostatic extension [17]. However, today, tumors are smaller and extensive extraprostatic spread is uncommon.

Incorporation of color or power Doppler modes to TRUS examination improves the detection of prostate cancer by identifying regions of hypervascularity but it has not yet been shown to improve staging accuracy [14, 18]. Recently, contrast-enhanced TRUS with microbubble has been reported to provide higher sensitivity for detection of cancer foci [9, 14]. Microbubbles are relatively large, micrometer-sized, gas-filled bubbles that can be seen with exquisite sensitivity with real-time US. Indeed, by using harmonic imaging and encoded phased imaging, single microbubbles can be detected [19]. Moreover, microbubbles can be coated with surface ligands, which preferentially target tumor neovascularity [19]. However, CE-TRUS has not yet been tested in a multi-institutional trial and no studies have been published on the application of microbubble in local staging disease [20]. Similarly, 3D TRUS is under investigation to im-

prove the identification of the cancer, delineation of prostate capsula in order to improve precision of prostate biopsy [21, 22].

### Computed Tomography

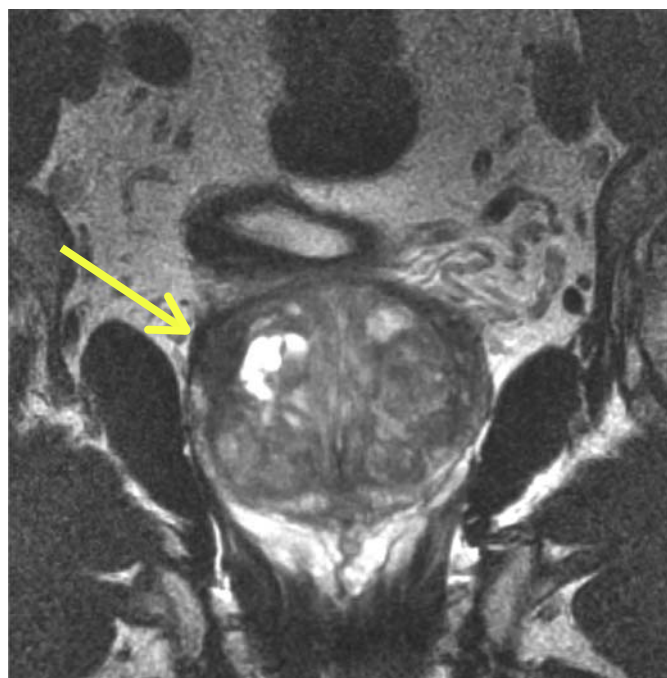
Despite the recent developments in multidetector CT (MDCT) technology, CT still has a very limited role in prostate cancer detection and staging [9, 14, 23]. CT has limited soft-tissue contrast resolution that is insufficient to distinguish the prostatic anatomy from adjacent structures (muscle, ligaments and bladder wall); it is usually impossible to identify tumors within the prostate gland unless they are larger. Despite high specificity (80–89%), CT sensitivity is reported to be very low (26–29%) in local staging [24, 25], also in patients planned to be treated with radiotherapy [26]. CT has no use in assessing clinically confined prostate cancer except for high-risk patients with clinically apparent, grossly advanced local disease (gross extracapsular disease, gross SVI, or invasion of the surrounding structures, including bladder, rectum, levator ani muscles, or pelvic floor) [9, 14].

### Magnetic Resonance Imaging

MRI provides the highest spatial resolution among the imaging modalities currently available and allows the best depiction of the internal zonal anatomy of the prostate as well as its contours. In addition, MRI also allows functional assessment with techniques such as magnetic resonance spectroscopy imaging (MRSI), dynamic contrast-enhanced MRI (DCE-MRI) and diffusion-weighted MRI (DWI-MRI). Therefore, MRI can be used for prostate cancer detection and staging [14, 20].

### Conventional Anatomical MRI Techniques

It is generally accepted that optimal MRI of prostate cancer requires the use of an endorectal coil and phased-array body coil on magnet with a field strength of at least 1.5 T. Clearly, the highest-quality MRI results from the combined use of endorectal coils and phased array body coils at 3T [9]. However, there are insufficient data in the literature to support the use of 3T MRI. Conventional MRI of the prostate gland includes  $T_1$ - and  $T_2$ -weighted (W) sequences.  $T_1$ W images are used to detect the presence of biopsy-related haemorrhage that is hyperintense compared with normal parenchyma.  $T_2$ W images provide depiction of the zonal anatomy of the prostate and are used to identify low signal areas in the peripheral zone. On MRI, the peripheral zone appears high in signal intensity on  $T_2$ W images and the central gland is lower and generally mixed in signal intensity. The central gland



**Fig. 1.** Coronal MR sequence FSE  $T_2$ W showing a prostatic lesion at the base of the right portion of the gland: an angulated prostate gland contour indicates the presence of an extraprostatic lesion ( $T_3a$ ) (arrow).

is separated from the peripheral zone by a hypointense pseudocapsula. The seminal vesicles are symmetric and appear as hyperintense on  $T_2$ W images. On  $T_2$ W images, cancers that arise in the peripheral zone are usually round or well-defined low signal intensity foci [27], while detecting prostate carcinoma in the central gland is difficult because the signal characteristics of this area usually overlap with those of the tumors [9, 14, 20, 28, 29]. Local MRI staging is accomplished by examining the presence and location of ECE and SVI. On  $T_2$ W images ECE can be detected by visualizing the direct extension of the tumor into the periprostatic fat; the secondary findings of ECE include asymmetry of the neurovascular bundle, tumor envelopment of the neurovascular bundle, an angulated prostate gland contour, an irregular or spiculated margin, capsular retraction and obliteration of the rectoprostatic angle [9, 14, 20, 30–33] (fig. 1). The features of SVI on MRI include demonstration of direct tumor extension from the base of the prostate into and around the seminal vesicle and/or the presence of focal low signal intensity within the seminal vesicle [9, 14, 30]. The combination of tumor at the base of the prostate that extends beyond the capsule and low signal intensity within a sem-

**Table 1.** MRI sensitivity and specificity in prostate cancer local staging

Authors	Pa-tients	Local staging	ECE	SVI	Sens, %	Spec, %
Sala et al. [30]	356	–	–	V	63	97
Bartolozzi et al. [34]	73	V	–	V	95 80	82 93
Cornud et al. [35]	175	–	V	–	69	95
Ikonen et al. [36]	51	V	–	–	60	63
		–	V	–	13	97
		–	–	V	59	84
Ikonen et al. [37]	44	V	–	–	50	65
		–	V	–	22	99
		–	–	V	50	90
May et al. [38]	54	–	V	–	80	97
		–	–	V	58	95
Perrotti et al. [39]	56	–	V	–	22	84
		–	–	V	23	93
Presti et al. [40]	56	V	–	–	97	58
		–	V	–	91	49
Rorvik et al. [41]	31	–	V		57	76
		–		V	71	83

ECE = Extracapsular extension; SVI = seminal vesicle invasion; V = evaluated; Sens = sensitivity; Spec = specificity.

inal vesicle that has lost its normal architecture is highly predictive of SVI [30]. Combined transverse, coronal, and sagittal sections facilitate evaluation of seminal vesicle and bladder neck invasion [31]. MRI has been reported to have 13–95% sensitivity and 49–97% specificity for detection of ECE and 23–80% sensitivity and 81–99% specificity for detection of SVI [30, 34–41] (table 1). The sensitivity and specificity for local staging with MRI vary considerably with technique and population: 14.4–100 and 67–100%, respectively [9]. Moreover, individual radiologist expertise is an important determinant of staging accuracy [42]. Two studies of the same patient population that used pathologic findings from a radical prostatectomy specimen as the standard of reference found that endorectal MR contributed significant incremental value to clinical variables in the prediction of ECE, although the contribution of MR was only significant when MR interpretation was performed by specialists in genitourinary MR as opposed to general body MR radiologists [43, 44]. The use of endorectal probe might allow more accu-

rate local staging even if recent studies showed a negative predictive value of only 50 and 61% for pT3 disease and seminal vesicle invasion [45] and, when compared with phased-array coil MRI, did not improve significantly the staging accuracy but resulted in more complications [46, 47]. Nowadays, MRI does not results sensitive in detecting minimal extracapsular extension even if the combination in specific nomograms of clinical and specific MRI findings may show benefits, mostly in the intermediate and high risk groups [48], while MRI remains an unnecessary but common practice in low-risk patients [49].

#### *Functional MRI Techniques (MRS, DCE-MRI, DWI)*

##### *Magnetic Resonance Spectroscopic Imaging (MRSI)*

MRSI is based on the detection of different metabolites that have characteristic resonant frequency (primarily determined by the chemical structure). MRSI provides information based on cellular metabolites within the prostate gland by providing the relative concentration of specific metabolites such as citrate, creatine, and choline. The normal prostate gland tissue (peripheral zone) contains low levels of choline and high levels of citrate, whereas prostate cancer shows high levels of choline and decreased levels of citrate. The increased choline levels in cancer are believed to be due to increased cell membrane turnover associated with cell proliferation, increased cellularity, and growth [9, 14, 50]. Other metabolites such as polyamines are reduced in tumors [9, 51]; however, polyamine peaks are difficult to be detected at 1.5 T. Currently, the increased choline-citrate ratio detected on MRSI is an indicator of malignancy. At 1.5 T the choline peak cannot be discriminated from the creatine peak and the ratio measured is really that of choline plus creatine to citrate (cho+cre/cit). The ratio of choline to citrate is related to the Gleason score, suggesting that MRSI may provide information about cancer aggressiveness. Integration of MRSI into routine prostate MRI practice has improved tumor detection rates in several studies [9, 14, 52]. Moreover, MRSI can help in the estimation of tumor volume which is considered, from histopathological studies, a significant predictor of extracapsular extension [32, 53]. Therefore, tumor volume estimates by MRSI have been used in conjunction with high-specificity MRI criteria to diagnose extracapsular spread and avoid a wide excision of the neurovascular bundles in most cases [54, 55] especially among less-experienced radiologists decreasing interobserver variability [42]. The metabolic mapping of the prostate tumor might be used, in a near future, to select the more appropriate surgical plan (neurovascular bundle preservation; risk of positive surgical margins) es-

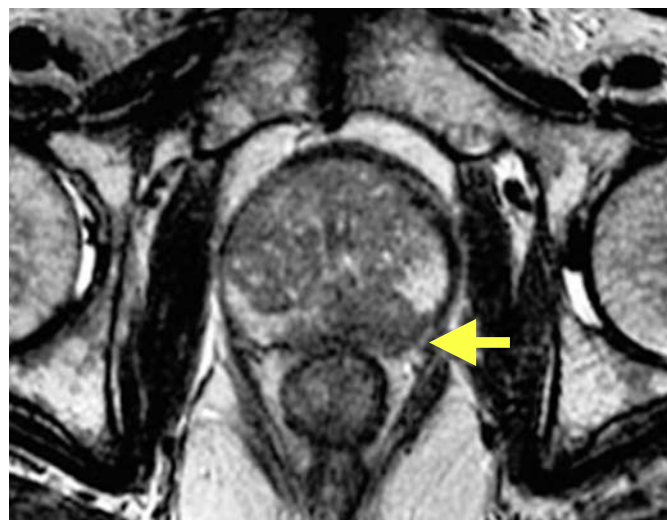
pecially with the use of 3T devices that allow faster acquisitions, smaller voxels and more accurate separation of metabolite peaks [56].

#### Dynamic Contrast-Enhanced MRI (DCE-MRI)

DCE-MRI evaluates the vascularity in tumors by following the time course of signal over time. Fast MR scanning sequences combined with the rapid injections of a low molecular weight contrast agent enable noninvasive imaging of tumor angiogenesis. Prostate cancer, like many tumors, demonstrates angiogenesis that can be detected on DCE-MRI. Prostate cancers show early, rapid enhancement and early washout on DCE-MRI. This pattern is highly predictive of prostate cancer but is not pathognomonic. However, smaller and low grade tumors may not demonstrate abnormal enhancement on DCE-MRI and several benign conditions such as prostatitis and post biopsy hemorrhage can mimic tumors on DCE-MRI [52, 57]. DCE-MRI can improve staging performance when used in conjunction with T<sub>2</sub>W images for less-experienced readers when compared to more-experienced readers [58]. Staging accuracy and, in particular, extracapsular extension need high spatial resolution, which is why imaging at 3T and the use of combined endorectal/body phased array coil are preferable [59, 60] (fig. 2). However, this method still suffers from a lack of standardization and has not been tested in multi-institutional large trials but only in small cases series where the combination of high-spatial-resolution DCE-MRI and T<sub>2</sub>W MRI improved prostate cancer staging (AUC 95% overall staging accuracy) compared with each technique alone [61].

#### Diffusion-Weighted MRI (DWI-MRI)

DWI-MRI provides qualitative and quantitative information reflecting tissue cellularity and cell membrane integrity. Generally, there is restricted diffusion in tumors, probably due to their higher cellular density. Qualitative assessment of relative signal attenuation at DW-MRI is used for cancer detection and characterization, while quantitative analysis of DW-MRI is achieved by calculation of the apparent diffusion coefficient. Prostate cancer lesions can be detected with DWI-MRI as region of restricted diffusion and appear as high signal intensity foci on DWI-MRI but are low in signal intensity on the apparent diffusion coefficient map [9, 14, 62]. As for other MRI techniques, DWI-MRI accuracy is significantly affected by the period between biopsy and the examination for the hemorrhage after the biopsy with contrasting opinions about the right timing [63–66] even if at least 2–3 weeks from the biopsy are recommended [67]. A recent study by



**Fig. 2.** Coronal sequence FSE T<sub>2</sub>W using a combined endorectal/body phased array coil in a 3-Tesla MRI: extracapsular extension in the left posterolateral part of the gland (arrow).

Kim et al. [68] reported an improvement in SVI prediction for 3T DWI-MRI in conjunction with T<sub>2</sub>W imaging compared with T<sub>2</sub>W imaging alone independently of the experience of the reader (AUC 0.81 vs. 0.69,  $p < 0.01$  for 3T DWI-MRI+T<sub>2</sub>W imaging and T<sub>2</sub>W imaging, respectively). DWI-MRI is still not in routine clinical use for prostate cancer staging even if recent technical advances in DWI-MRI, including improved spatial resolution, appear promising.

#### Positron Emission Tomography/Computed Tomography

PET shows molecular function and activity that is not available with CT. PET/CT is emerging as an important noninvasive, whole-body imaging modality for prostate cancer evaluation. Integrated PET/CT improves image interpretation because the fused images can enable the physician to associate increased metabolism with its anatomical location. PET uses compounds labeled with positron-emitting radioisotopes to detect pathologic processes [69]. The most common available PET tracer is <sup>18</sup>F-fluoro-2-deoxy-2-D-glucose (FDG) which is an indicator of glycolytic activity in cancer cells. Cancers have increased metabolism and utilize the less-efficient glycolytic pathway, both of which lead to increased glucose analogue uptake [70]. Increased glucose uptake and metabolism in tumors are facilitated by an elevated expression of glucose transporters, which has been shown in

**Table 2.**  $^{11}\text{C}$ (carbon)-choline PET/TC sensitivity in prostate cancer local staging

Authors	Pa-tients	PET/TC	Local tumor	ECE
Eschmann et al. [86]	42	$^{11}\text{C}$ -Cho	96.6 78.4	NV
Martorana et al. [89]	43	$^{11}\text{C}$ -Cho	NV	22
Rinnab et al. [87]	55	$^{11}\text{C}$ -Cho	NV	36
Farsad et al. [88]	36	$^{11}\text{C}$ -Cho	66	
Beheshti et al. [90]	130	$^{11}\text{C}$ -Cho	NV	45

NV = Not valuated.

several cancers [71–76]. However, FDG is not recommended for the diagnosis and staging of localized prostate cancer because of the low metabolic glucose activity of prostate cancer. A further drawback is that the normal urinary FDG excretion results in high bladder activity that can mask prostate tumors [9, 14, 77–80]. To improve the usefulness of PET/CT several additional radiotracers have been extensively studied, including  $^{11}\text{C}$ -acetate,  $^{11}\text{C}$ -choline,  $^{18}\text{F}$ -fluorocholine ( $^{18}\text{F}$ -FCH),  $^{11}\text{C}$ -methionine,  $^{18}\text{F}$ -fluoride, anti-1-amino-3- $^{18}\text{F}$ -fluorocyclobutane-1-carboxylic acid (anti- $^{18}\text{F}$ -FACBC), fluoro-dihydrotestosterone ( $^{18}\text{F}$ -FDHT) and  $^{18}\text{F}$ -fluorothymidine ( $^{18}\text{F}$ -FLT) [9, 14]. Valid results were obtained with choline labeled with  $^{11}\text{C}$  or  $^{18}\text{F}$ , which is the major phospholipid in the cell membrane [81]. Choline kinase activity is upregulated in tumor cells [82, 83]. Bowel and bladder activity can only occasionally be observed even if the short half-life of  $^{11}\text{C}$  limits its use and, to overcome this problem, an F-labeled choline tracer ( $^{18}\text{F}$ -fluorocholine) was developed as an alternative [84].  $^{18}\text{F}$ -FDG PET did not give good results in local staging even if tracer uptake is higher in poorly differentiated tumors and higher PSA values [85].  $^{11}\text{C}$ -choline PET/TC, even if helpful in detecting primary prostate cancer [52], demonstrated low sensitivity for the assessment of extraprostatic extension [86–90] (table 2). Martorana et al. [89], comparing  $^{11}\text{C}$ -choline PET/TC with MRI for extraprostatic extension, showed a very low sensitivity (22 vs. 63%,  $p < 0.001$ ). Rinnab et al. [87], in a small cohort of patients, compared  $^{11}\text{C}$ -choline PET/TC to TRUS showing how, even if superior to TRUS, PET/TC tended to understage prostate cancer in terms of local extension of the disease. Beheshti et al. [90] obtained better results with  $^{18}\text{F}$ -fluorocholine PET/TC in a prospective study on 132 patients. However,

further studies in large population of patients are still necessary to establish its clinical role in the local staging of prostate cancer.

## Metastases

### Nodal Disease

The presence of lymph node metastases is a strong predictor of disease recurrence and progression and it also directly affects treatment selection. Imaging for lymph node metastases is necessary for men who are at higher risk of metastases, particularly those with PSA level greater than 20 ng/ml, Gleason score greater than 7 and/or clinical tumor stage T3 or higher [91]. Nomograms based on clinical data (PSA level, Gleason grade, DRE findings) provide risk stratification estimates that guide the appropriate ordering of imaging tests [92, 93]. Cross-sectional imaging (CT and MRI) of the lymph nodes has been widely used in clinical practice. However, the ability of these techniques to distinguish benign and malignant lymph nodes is mainly based on node size ( $>1$  cm) [9–11, 14, 94]. CT and MRI are both poorly able to identify involved nodes because nodal metastases are often small or microscopic and nodal enlargement due to metastases occurs relatively late in the progression of prostate cancer (fig. 3). A meta-analysis has shown that CT and MRI have both a sensitivity of  $\sim 40\%$  and a specificity of  $\sim 80\%$  to detect lymph node metastases [95] (table 3). The use of lymphotropic ultrasmall superparamagnetic particles of iron oxide (USPIO) as a contrast agent ('Combidex') for MRI may help to improve detection of nodal metastases by characterizing lymph node architecture, independently from their size. USPIO particles are consumed by macrophages in normal lymph nodes resulting in a signal decrease on  $T_2/T_2^*W$  MRI sequences. This technique increased the sensitivity to 90.5% even if node-by-node comparison between the pre- and post-USPIO images renders interpretation time consuming (80 min) [94, 96, 97]. The combination of DWI and USPIO-enhanced MRI did not increase accuracy (90%) but resulted in a reduction of over 1 h in image analysis [98]. However, the drug 'Combidex' was ultimately rejected for approval by the FDA here and has also met the same fate in Europe. The company producing the drug has stopped all production of it. The application of PET or PET/CT to image lymph nodes, using several different tracers, has been investigated as a staging technique. The advantage of PET over CT and MRI is its ability to detect metabolic changes of tumors cells in a structurally normal lymph node before

**Table 3.** MRI and CT sensitivity (Sens) and specificity (Spec) in detecting lymph node metastases from prostate cancer [95]

Authors	Patients	Sens, %	Spec, %
CT			
Hricak	85	25	99
Engeler	160	5	100
Van Poppel	285	77	96
Flanigan	173	27	97
Weinermann	19	68	75
MRI			
Bezzi	51	68	94
Rifkin	185	6	95
Jager	63	59	97
Perotti	56	13	90
Harisinghani	80	46	78

tumor cells enlarge this lymph node. Since 2003 different authors investigated the role of choline PET/TC in PCa staging reporting a wide variability in sensitivity (0–100%), high specificity (95–100%) and PPV (75–90%) [99–104] (table 4). These results might be due to population selection or small number of lymph node-positive patients studied. At present, routine clinical use of choline PET/TC cannot be recommended even if good specificity and PPV might lead to the use of the examination in selected high risk patients in order to avoid the number of negative and inconclusive procedures and reduce the costs. Large prospective cost-effectiveness studies should be performed in order to assess the real usefulness of Choline PET-TC.

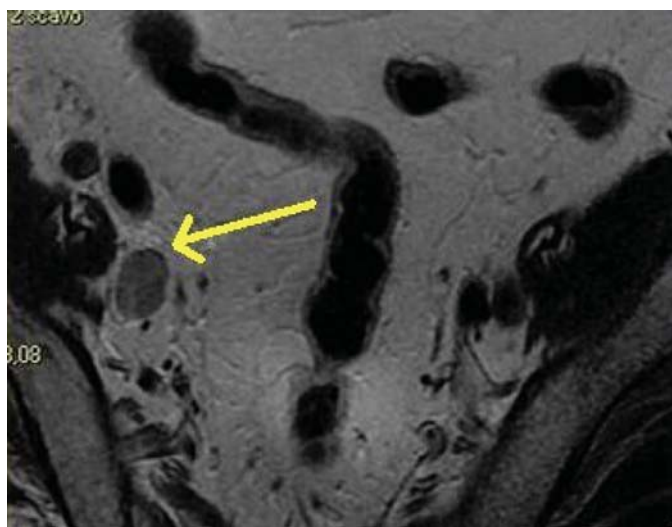
#### Metastatic Bone Disease

Bone is the most common site of PCa metastases accounting for as much as 80% of all metastases [105]. Spread occurs via the hematogeneous route to well-vascularized areas of the skeleton (the axial skeleton is the initial and preferred site) determining preferentially osteoblastic lesions [105]. Bone scintigraphy continues to be the mainstay of diagnosis of initial spread of cancer to bone [106]. In 1990, it was proposed that routine bone scans should not be used for patients with PSA below 10 ng/ml [107, 108]. The most recent EAU guidelines state that bone scintigraphy may not be indicated in asymptomatic patients if the serum PSA level is less than 20 ng/ml in the presence of well or moderately differentiated tumours (grade B recommendation) [106].

**Table 4.** Choline PET/TC sensitivity, specificity and positive predictive value in detecting lymph node metastases from prostate cancer

Authors	Patients	Radio-pharm.	Sens, %	Spec, %	PPV, %
Budiharto et al. [104]	36	<sup>11</sup> C-Cho	9.4	99.7	75
De Jong et al. [99]	67	<sup>11</sup> C-Cho	80	96	–
Schiavina et al. [100]	57	<sup>11</sup> C-Cho	60	98	90
			41	100	94
Beheshti et al. [101]	111	<sup>18</sup> F-Cho	45	96	82
			66*	96*	82*
Steuber et al. [102]	20	<sup>18</sup> F-Cho	0	100	–
Poulsen et al. [103]	25	<sup>18</sup> F-Cho	100	95	75

\* For lymph nodes metastases  $\geq 5$  mm in diameter. Sens = Sensitivity; Spec = specificity; PPV = positive predictive value; <sup>11</sup>C-Cho = carbon 11-choline; <sup>18</sup>F-Cho = fluoro 18-choline.

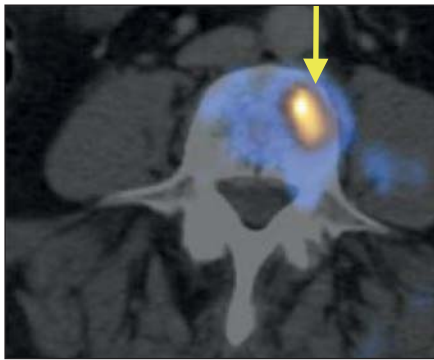
**Fig. 3.** Coronal 1.5-Tesla MRI sequence showing a lymph node metastasis from prostate cancer in the right obturator fossa in a patient with advanced disease (arrow).

However, because bone scintigraphy images the secondary effect of the tumor on the skeleton (osteoblastic reaction) rather than tumor proliferation, false positives occur from trauma and various other non-cancerous sources and, moreover, microscopic infiltrations and osteolytic lesions are not detected leading to limited sensitivity and specificity [20, 109, 110]. Moreover, in patients with prostate and breast cancer, a 'flare' phenomenon may be observed, where uptake initially increases after

**Table 5.** Sensitivity and specificity of new tracers ( $^{18}\text{F}$ -fluoride or  $^{18}\text{F}$ -fluoromethylcholine)-PET for detection of bone metastases from prostate cancer

Authors	Patients	BS Sens/Spec, %	$^{18}\text{F}$ -Fluoride PET Sens/Spec, %	$^{18}\text{F}$ -Fluoride PET/TC Sens/Spec, %	FCH PET Sens/Spec, %
Even-Sapir et al. [127]	44	57/57 39/83	100/62 100/79	100/100 100/100	–
Withofs et al. [128]	34	45/79	–	76/84	–
McCarthy et al. [129]	26	–	–	–	96/96

BS =  $^{99\text{m}}\text{Tc}$ -methylene diphosphonate ( $^{99\text{m}}\text{Tc}$ -MDP) planar bone scintigraphy; FCH PET =  $^{18}\text{F}$ -fluoromethylcholine positron emission tomography.



**Fig. 4.**  $^{11}\text{C}$ -choline PET/CT showing a vertebral bone metastasis from prostate cancer: the high concentration of the agent is evident in the lateral part of the vertebral bone (arrow).

chemotherapy or hormone therapy, peaking at 6 weeks after treatment as bone turnover increases as part of the healing process [111, 112]. In this setting, the sensitivity of bone scintigraphy in detecting a response to therapy remains questionable. Care must be taken in this situation to avoid mistaking apparent new lesions for areas of new metastatic disease, when subtle changes were in fact present in prior studies.

Because of the limitations of bone scintigraphy imaging modalities such as plain radiography, CT, MRI, PET are needed to clarify equivocal lesions. At plain radiography lesions are predominately sclerotic appearing nodular, rounded and fairly well circumscribed in CaP, while CT shows both osteolytic and osteoblastic lesions with sensitivity ranging from 71 to 100% [109].

MRI is potentially the technique of choice in detecting prostate bone metastases because of its high spatial resolution and its excellent soft tissue contrast. Small metastatic deposits in the bone and bone metastasis without

cortical involvement may be seen earlier on MRI than on bone scans [109, 113]. Metastases to bone marrow leads to a lengthened  $T_1$  relaxation time and signal loss, which contrast with the surrounding high signal marrow fat [109]. Conventional MRI covers the whole spine and pelvis (in which the majority of prostate cancer metastases arise) in few minutes and it is possible to include femoral necks that are at risk of pathological fracture. Moreover, with newer scanners whole-body MRI is possible in less than 15 min [20, 109]. One prospective study has shown that MRI has a sensitivity of 100% and a specificity of 88% to detect bone metastases [114]. DCE-MRI and DWI have shown potential in detecting metastatic bone disease and monitoring response to therapy in several tumors but their use in metastatic bone disease from PC is in its infancy [20, 115, 116].

Single photon emission computed tomographic (SPECT) studies of the skeleton have been shown to be more sensitive in the detection of metastatic disease than planar images alone and are usually performed when symptoms or clinical suspicion for disease are present, particularly bone pain. SPECT has a higher accuracy than bone scintigraphy for vertebral lesions but is not widely used [117–119]. Combined SPECT/CT, a recent development, adds anatomic information to SPECT, and its incremental value to SPECT is yet to be evaluated [120].

FDG PET/CT imaging has limitations with regard to distinguishing tumors from inflammation [121]. Sensitivity of FDG-PET for detecting prostate cancer metastatic to bone varied between 18 and 75% [20] and is considered to be inferior to bone scintigraphy for prostate cancer [122, 123]. However, an advantage of FDG-PET over bone scintigraphy is its ability to identify also non-skeletal metastatic disease, local recurrence and distant spread after treatment failure [115, 123]. Moreover, in pa-



tients with metastatic disease receiving chemotherapy, an important role of PET imaging may lie in its ability to evaluate early treatment response [20]. Future applications of PET will therefore involve new tracers, which are currently under clinical investigation. One of these tracers is  $^{11}\text{C}$ -methionine which differentiates tumor from normal tissue due to elevated protein synthesis [124, 125]. Other  $^{11}\text{C}$ -labeled PET agents include  $^{11}\text{C}$ -acetate and  $^{11}\text{C}$ -choline, both of which have shown promise in imaging prostate cancer metastases [20, 126] (fig. 4). Other new tracer are being developed such as  $^{18}\text{F}$ -fluroide or  $^{18}\text{F}$ -fluoromethylcholine, showing good sensitivity and specificity values superior to bone scintigraphy even if current clinical practice might be modified only with more data available [127–129] (table 5).

Another important discovery is that the use of multiple tracer studies in the same patient frequently displays the heterogeneity of tumor biology. Patients who receive  $^{11}\text{C}$ -methionine and FDG scans on the same day may display metastases that are positive for both tracers,  $^{11}\text{C}$ -methionine only or FDG only [125]. The optimal choice of radiotracers for tumor diagnosis and follow-up depends on the organ site. Nevertheless, the concept of using PET with multiple radiotracers that answer different questions is likely to become an important thrust in the future of metabolic prostate cancer imaging [125, 130]. In the future, molecular imaging will influence prostate cancer more and more as new tracers are developed, including antibodies that target important prostate-specific molecules such as prostate-specific membrane antigen. Gene expression imaging and imaging of cell trafficking during adoptive immunotherapy are on the near horizon.

## Conclusions

To date, the role of imaging in prostate cancer staging is not well established yet, even if considerable advances have been made, particularly in functional imaging. The classic morphological imaging modalities, such as CT and MRI, lack of sensitivity, especially in detecting minimal extracapsular extension and lymph node minimal involvement which are the most challenging problems to be solved in order to choose the more appropriate therapeutic approach. Functional MRI, especially with the use of new 3T devices, and PET-TC, with the introduction of new radiotracers, seem to be promising tools for PC local and distant staging, even if lack of standardization, high costs, limited availability and absence of multi-institutional large trials limit their use in high-risk patients or in clinical trials. Another important discovery is that the use of multiple tracer studies in the same patient, displaying the heterogeneity of tumor biology and answering different questions, is likely to become an important thrust in the future of metabolic prostate cancer imaging. As for diagnosis, also for staging, one of the difficulties with a rapidly developing technology is that as results are published newer generations of equipment emerge, making the last data appear obsolete. However, it is important to critically review publications periodically, redirect research questions as necessary, thus avoiding the risk of not understanding completely the relevance and the potential of a technology.

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