

Imaging and evaluation of patients with high-risk prostate cancer

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Abstract | Approximately 15% of men with newly diagnosed prostate cancer have high-risk disease. Imaging is critically important for the diagnosis and staging of these patients, and also for the selection of management. While established prostate cancer staging guidelines have increased the appropriate use of imaging, underuse for high-risk prostate cancer remains substantial. Several factors affect the utility of initial diagnostic imaging, including the variable definition of high-risk prostate cancer, variable guideline recommendations, poor accuracy of existing imaging tests, and the difficulty in validating imaging findings. Conventional imaging modalities, including CT and radionuclide bone scan, have been employed for local and metastatic staging, but their performance characteristics have generally been poor. Emerging modalities including multiparametric MRI, positron emission tomography (PET)–CT, and PET–MRI have shown increased diagnostic accuracy and could improve accuracy in staging patients with high-risk prostate cancer.

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Introduction

In 2015, approximately 220,800 men will be diagnosed with prostate cancer in the USA—accounting for 27% of all cancer diagnoses in men in this country.¹ Prostate cancer varies widely in aggressiveness, therefore, accurately predicting how life expectancy and quality of life might be affected by the disease is vital to its management. Approximately 15% of men with prostate cancer are diagnosed with high-risk disease and are at increased risk of treatment failure and mortality.² A number of risk-stratification schemes for prostate cancer have been devised, but controversy exists as to the definition of high-risk prostate cancer.³ Recommendations regarding the use of imaging vary widely depending on the guidelines used by the clinician. Of men with newly diagnosed prostate cancer, 80% will have localized disease, 12% will have regional disease, and 4% will have distant disease.⁴ However, for newly diagnosed high-risk prostate cancer, 22% of men will have a positive bone scan, 31% will have a positive abdominal CT, and 33% will have a positive pelvic CT on initial diagnostic imaging, highlighting the importance of imaging in the initial diagnosis of high-risk prostate cancer.⁵ Several factors affect the utility of initial diagnostic imaging, including the variable definition of high-risk prostate cancer, the relatively poor diagnostic accuracy of existing imaging tests, and the difficulty in validating imaging findings. Guidelines for imaging men with newly diagnosed prostate cancer have been established, but they have not been universally adopted.^{6,7} Barriers to adoption include the

multiplicity of imaging guidelines as well as challenges in disseminating hospital-level data on use and ongoing guideline updates to physicians.

The goals of initial diagnostic imaging evaluation can include identification and localization of occult metastatic disease (in lymph nodes and bone), assessment of resectability and/or curability, and prediction of local morbidity. Conventional imaging modalities, including CT and radionuclide bone scan, have demonstrated poor performance characteristics, often requiring correlation with MRI or bone biopsy in the event of solitary or equivocal abnormalities. Emerging noninvasive imaging technology and radiopharmaceuticals, such as multiparametric MRI (mpMRI), positron emission tomography (PET)–CT, and PET–MRI could improve staging through increased diagnostic accuracy.

In this Review, we provide a summary of the definitions of high-risk prostate cancer and highlight the trends in the use of imaging for initial staging. We discuss the current imaging modalities available for evaluation of newly diagnosed high-risk prostate cancer, and include insight on using imaging modalities on disease recurrence and for surveillance when appropriate, and present emerging imaging modalities which could have improved performance characteristics.

Defining high-risk prostate cancer

Currently, most acknowledged criteria used to risk stratify prostate cancer are based on clinical stage, biopsy Gleason score, and pretreatment serum PSA level. No single criterion can precisely identify all men at high risk of disease progression and mortality after local therapy. Various risk classification systems that incorporate these three factors have been developed, but standardized

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Competing interests

S.S.T. has been a speaker for Eigen, a consultant for Hitachi-Aloka Medical and HealthTronics, and a sponsored trial investigator for Trod Medical. All other authors declare no competing interests.

Key points

- Imaging high-risk prostate cancer is predominantly conducted using radionuclide bone scan, CT, and MRI
- Multiparametric-MRI (mpMRI) and positron emission tomography (PET)-CT, using novel imaging techniques and radiopharmaceuticals, are currently being investigated and incorporated into clinical use
- mpMRI and PET-CT are more advanced approaches than conventional techniques and offer improved sensitivity and specificity, enabling more accurate assessment of disease
- Integrated PET-MRI could provide a comprehensive assessment of local disease extent, lymph nodes, and bones, as well as functional assessment of tumour aggressiveness and prognosis
- Continued studies are warranted to further establish the role of new modalities in the management of patients with high-risk prostate cancer

criteria that define high-risk prostate cancer are still lacking (Box 1).^{8–15} This lack of consensus is a critical obstacle for patient counselling, evaluation of treatment outcomes, and design of clinical trials, as well as the establishment and appraisal of guidelines that include recommended staging protocols.

High-risk, clinically localized prostate cancer has classically been defined by D'Amico *et al.*⁸ as any combination of a PSA level >20 ng/ml, a Gleason score of ≥8, or clinical stage ≥T2c (Box 1). The American Urological Association (AUA) and the National Institute for Health and Care Excellence (NICE) in the UK have endorsed the D'Amico high-risk prostate cancer criteria.^{11,16} The European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) guidelines have narrowed this risk group by restricting the clinical stage criterion to ≥T3a.^{9,15} Interestingly, the role of T clinical stage remains controversial in stratifying prostate cancer, as it does not necessarily add information and has high interobserver variability.¹²

Box 1 | Used definitions of high-risk prostate cancer

D'Amico *et al.*⁸

PSA ≥20 ng/ml or Gleason score ≥8 or clinical stage ≥T2c

UK National Institute for Health and Care Excellence¹⁶

PSA ≥20 ng/ml or Gleason score ≥8 or clinical stage ≥T2c

American Urological Association¹¹

PSA ≥20 ng/ml or Gleason score ≥8 or clinical stage ≥T2c

European Association of Urology¹⁵

PSA ≥20 ng/ml or biopsy Gleason score ≥8 or clinical stage ≥T3a

National Comprehensive Cancer Network⁹

PSA ≥20 ng/ml or Gleason score ≥8 or clinical stage ≥T3 or any two of the following: T2b/c, Gleason score ≥7, PSA 10–20 ng/ml

Radiation Therapy Oncology Group¹⁰

PSA 20–100 ng/ml, biopsy Gleason score ≥8, and any clinical stage, or clinical stage ≥T2c or PSA <100 ng/ml

Cancer of the Prostate Risk Assessment (CAPRA) score¹⁷

Combination score in which a value is given to variables including age, PSA value, clinical stage, biopsy Gleason score, and percentage of positive biopsy cores. A final score of >6 for all summed variables means the patient is deemed high risk

European Society for Medical Oncology¹³

Any one of PSA >20 ng/ml, Gleason score >7, clinical stage T3 or T4

American College of Radiology¹⁴

PSA ≥20 ng/ml or Gleason score ≥8 or clinical stage ≥T2c

The Cancer of the Prostate Risk Assessment (CAPRA) score incorporates additional variables into the equation, which include, age, PSA level, clinical stage, biopsy Gleason score, and percentage of positive biopsy cores. A CAPRA score between six and ten represents high-risk prostate cancer.¹⁷ This stratification scheme has been shown to predict prostate-cancer-specific mortality independently of the treatment given.¹⁸ Furthermore, adding secondary parameters, such as the extent of cancer in needle biopsy, prediagnosis PSA velocity, PSA doubling time, or the presence of a tertiary Gleason pattern, has been proposed to enhance risk stratification.^{19–21} The applicability of some of these parameters remains unclear, as they are not routinely collected in clinical practice. An optimal definition of high-risk prostate cancer should ultimately be a balance that favours high sensitivity, whereby all patients with locally advanced or occult metastatic disease are included, with an acceptable level of specificity, whereby most patients with otherwise organ-confined disease are excluded.

Imaging in high-risk prostate cancer

Staging prostate cancer is important not only for prediction of prognosis, but also for providing a balanced approach to treatment selection (Figure 1). The desire to treat and cure must be balanced against the known morbidity of treatment and effects on quality of life. Selection of patients for local, radical therapy should rely on a reasonable expectation of potential for cure or avoidance of local morbidity. Currently, radionuclide bone scan, CT, and MRI are the most commonly used modalities in the staging of newly diagnosed prostate cancer. To facilitate optimal imaging of newly diagnosed prostate cancer, the NCCN established clear imaging guidelines in 1996 for men with incident prostate cancer clarifying the role of imaging in the staging evaluation.²² The AUA issued a best practice statement in 2000, which recommended pretreatment staging of prostate cancer only in the setting of high-risk disease, with updates in 2007 and 2011.²³ The NCCN and AUA consensus statements use PSA level, biopsy Gleason grade, presence of symptomatic bone pain, and clinical stage to predict the yield of imaging studies.²⁴ Other professional societies involved in the management of prostate cancer, such as the American Society of Clinical Oncology, the American Society for Therapeutic Radiology and Oncology, and the American Cancer Society, do not have specific recommendations for the use of initial diagnostic imaging radiographic screening.²⁴

Guidelines for initial diagnostic imaging in a patient with newly diagnosed high-risk prostate cancer are organization dependent (Table 1).^{9,25} Most organizations support a radionuclide bone scan for the initial staging of high-risk prostate cancer, but not all specifically address imaging for soft tissue metastases (Table 1).^{26,27} Those that do commonly endorse a pelvic CT or MRI.

In 2012, the American Society of Clinical Oncology (ASCO) and the AUA again highlighted the need to reduce imaging for low-risk prostate cancer in the

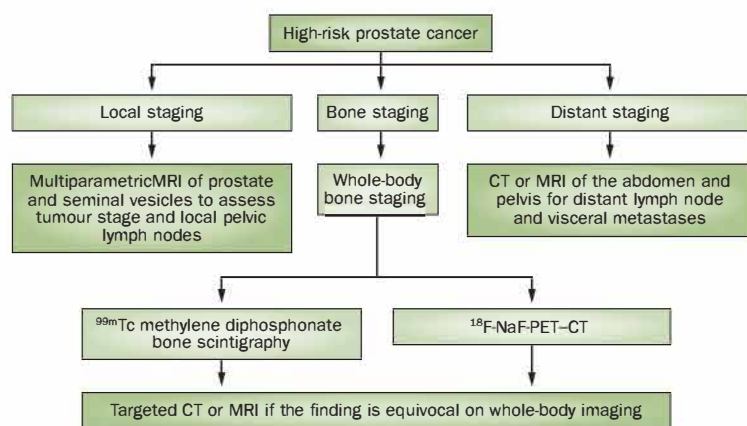


Figure 1 | An algorithm for imaging patients with high-risk prostate cancer. Local staging is performed with multiparametric MRI and CT or MRI is employed for evaluation of distant metastases. In men whose bone scintigraphy results are equivocal, ^{18}F -FDG-PET-CT, targeted CT, or MRI can be used for additional clarification. Abbreviations: FDG, fluorodeoxyglucose; PET, positron emission tomography.

'Choosing Wisely' campaign, a multidisciplinary effort to reduce medical testing, decrease overuse of health-care resources, and improve quality of care.²⁸ Several studies show poor compliance with these guidelines. Analysis of Surveillance, Epidemiology, and End Results (SEER)-medicare data has demonstrated that 45% of men with low-risk prostate cancer receive imaging that is not adherent to guidelines and only 66% with high-risk disease receive guideline-adherent imaging.⁷ Similar trends have been observed in the Veteran's Health Administration population, where 41% of men with low-risk prostate cancer underwent imaging whereas only 30% with high-risk prostate cancer received imaging.²⁹ Imaging is often paradoxically underused in the high-risk subgroup of patients, who could potentially benefit from it the most. The association between higher imaging rates and increasingly aggressive disease risk characteristics suggest that established guidelines have had limited effect on the high rates of inappropriate imaging. The publication of guidelines seems to lower national rates of inappropriate imaging, but it also lowers the rate of appropriate prostate cancer imaging.³⁰ The reason driving this decrease in use of imaging is not clear, but the practice pattern has been observed in several studies.^{6,31} Factors leading to the discrepancy between guidelines and clinical practice include lack of awareness or confidence in the scientific foundation of best practice statements, financial incentives, regional variation, and variability of physician practice patterns.

Current modalities for local staging CT and MRI

CT and MRI are noninvasive methods for assessing the prostate and surrounding structures that enable local staging of high-risk prostate cancer. Accurate local staging with imaging is relevant for treatment selection and surgical planning and bladder neck invasion. MRI is the only examination with sufficient accuracy to be used

in clinical practice for the identification of extraprostatic extension (EPE) and seminal vesicle involvement (SVI), given its combination of high spatial resolution and contrast resolution. Historically, assessment for EPE on MRI was based on T2-weighted imaging (T2WI) as it has high spatial resolution and enables the best visualization of prostate anatomy among clinical pulse sequences, including the prostate capsule. Various observations on T2WI for determining EPE have been explored, but none individually achieved both high sensitivity and high specificity. Commonly used T2WI observations in clinical practice include irregular capsular bulge, asymmetry of the neurovascular bundle, and obliteration of the rectoprostatic angle (Figure 2).³² An additional finding that has been described as useful for detection of EPE is broad capsular abutment of the dominant lesion, even in the absence of direct visualization of EPE, with one expert panel suggesting contact of 1.5 cm as a threshold for predicting EPE.³³

Even though these useful findings have been described, identification of EPE on T2WI alone remains difficult. Other studies have shown improved accuracy for EPE detection when combining T2WI with either diffusion-weighted imaging (DWI)³⁴ or dynamic-contrast-enhanced (DCE) imaging,³⁵ as these additional sequences improve localization of the dominant tumour, and this information in turn helps to predict the presence of EPE.

Hardware-related factors also improve prediction of EPE. For instance, imaging using a 3T system has been shown to contribute to high performance in the detection of EPE.³⁶ In addition, detection of EPE has been reported to be more accurate using an endorectal coil than a pelvic phased-array coil.³⁷ To this end, an expert panel has recommended using an endorectal coil when performing prostate MRI for local staging, regardless of magnet field strength.³³ Previous literature has shown improved accuracy for localized EPE using an endorectal coil, but increasing availability of 3T systems and ongoing improvements in other aspects of MRI hardware (both at 1.5T and 3T), have led to improved quality of nonendorectal coil exams, and the American College of Radiology "Prostate Imaging and Reporting and Data System: Version 2" guidelines, released in 2015, do not require the use of an endorectal coil.³⁸

Currently, using modern magnetic resonance hardware and state-of-the-art multiparametric protocols, high performance of MRI for detecting of EPE has been reported. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of mpMRI in determining EPE in high-risk prostate cancer have been reported to be 64.9%, 72.7%, 88.9%, and 38.1%, respectively.³⁹ In patients with high-risk disease, a high PPV is important, as knowledge of the site of EPE might help in reducing the risk of a positive surgical margin. Combining both direct and indirect signs of EPE on mpMRI increases the sensitivity and specificity to 83% and 99%, respectively.⁴⁰ However, the accuracy of mpMRI for EPE is still influenced by the extent of extraprostatic tumour beyond the capsule. Very high

Table 1 | Clinical guidelines for staging prostate cancer

Clinical guidelines (year)	Imaging for bone metastases		Imaging for soft tissue metastases	
	Criteria	Modality	Criteria	Modality
National Comprehensive Cancer Network (2015) ⁹	cT1 disease and PSA >20 ng/ml or cT2 disease and PSA >10 ng/ml or Gleason score ≥8 or cT3/T4 disease, symptomatic	Bone scan	T3 or T4 or T1-T2 and a nomogram-indicated probability of lymph node involvement >10%	Pelvic CT or MRI
UK National Institute for Health and Care Excellence (2014) ¹⁸	When hormonal therapy is being deferred through watchful waiting to asymptomatic men who are at high risk of developing bone complications (2008) Do not routinely offer to men with low-risk localized disease (2008)	Bone scan	Histologically-proven prostate cancer if knowledge of tumour or lymph node could affect management	MRI or CT if MRI is contraindicated
European Association of Urology (2015) ¹⁵	Gleason score ≥8, or ≥cT3/T4, or PSA >10 ng/ml, or symptomatic	Bone scan, in equivocal cases can use ¹¹ C-choline-PET-CT, ¹⁸ F-NaF-PET-CT, or whole-body MRI	Gleason score ≥8, or ≥cT3/T4, or PSA >10 ng/ml, or symptomatic	CT or MRI for distance metastases; mpMRI should be used in local staging
Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence Group (2014) ²⁶	Scan patients with high-risk and intermediate-risk disease who have at least two of the following: PSA >10 ng/ml, Gleason score ≥7, or palpable disease (≥cT2b)	Bone scan	NA	NA
American College of Radiology (2013) ¹⁴	PSA ≥20 ng/ml or Gleason score 8–10 or clinical stage ≥T2c	Bone scan (a score of 8 out of 10 is classed as usually appropriate), whole-body ¹⁸ F-FDG-PET-CT (a score of 4 out of 10 is classed as usually not appropriate)	PSA ≥20 ng/ml or Gleason score 8–10 or clinical stage ≥T2c	mpMRI (a score of 8 out of 10 is classed as usually appropriate), CT (a score of 7 out of 10 is classed as usually appropriate), whole-body ¹⁸ F-FDG-PET-CT (a score of 4 out of 10 is classed as usually not appropriate)
European Society for Medical Oncology (2013) ¹³	cT3 or cT4 or Gleason score >7 or PSA >20	Bone scan	T3 or T4 or Gleason score >7 or PSA >20	MRI of the pelvis should be considered
American Urological Association (2011) ²⁵	PSA ≥20 ng/ml or Gleason score ≥8 or ≥cT2c	Bone scan and CT	NA	NA
Briganti's Classification and Regression Tree (2010) ²⁷	Gleason score ≥8 or ≥cT2 disease and PSA >10 ng/ml, or symptomatic	Bone scan	NA	NA

Abbreviations: mpMRI, multiparametric-MRI; PET, positron emission tomography. Adapted from *Urology* 83, Crawford, E. D. et al. Challenges and recommendations for early identification of metastatic disease in prostate cancer. 664–669 (2014), with permission from Elsevier.

sensitivity has been reported in two studies published in 2013 and 2014 for established EPE in general or EPE of at least 2 mm;^{41,42} however, sensitivity remains relatively limited for lesser extension beyond the prostate, which is characterized as focal in nature. Accurate detection of EPE also continues to require reader experience, with studies consistently demonstrating stronger performance for readers with more experience.^{43,44}

SVI has also been evaluated using T2WI. SVI appears on the scan as a T2-hypointense mass within the seminal vesicles, typically in direct contiguity with the tumour in the prostate base (Figure 3). Various processes can contribute to false-positive findings for SVI, including fibrosis and/or scarring in the seminal vesicles, or rare causes such as amyloidosis.⁴⁵ A false-negative interpretation can occur owing to microscopic extension of the tumour into the seminal vesicles via the ejaculatory duct. Studies have shown improved accuracy for detecting SVI when T2WI and DWI are combined and include apparent diffusion coefficient (ADC) maps.⁴⁶ High sensitivity and specificity for SVI (83% and 99%, respectively) have been observed using mpMRI.⁴⁰

The decision of whether to locally stage prostate cancer is dependent on the intent of therapy. For men with metastatic disease, local staging might have limited influence on treatment management. In the event that surgery is contemplated, then a prostate MRI is—in our opinion—highly valuable and supported by existing literature.^{47,48}

Molecular imaging

In the past two decades, with the advent of PET and PET-CT, additional options for prostate cancer staging have become available. ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) is the most widely used PET-CT radiotracer in oncologic imaging. ¹⁸F-FDG usually takes advantage of the increased consumption of glucose, which is a characteristic of most tumour cells and is partially related to overexpression of the GLUT-1 glucose transporters and increased hexokinase activity.⁴⁹ However, it has limited sensitivity for prostate cancer as most tumours show high differentiation and, therefore, do not take up ¹⁸F-FDG to a large extent. Increased ¹⁸F-FDG uptake and accumulation is regularly only found in dedifferentiated, aggressive, and

metastasized prostate cancer. Additionally, the urinary excretion of ^{18}F -FDG results in this tracer accumulating in the ureters and urinary bladder, obscuring the view of the prostate. Another PET-CT radiotracer that has been studied is acetate, which, despite its higher sensitivity for prostate cancer cells than ^{18}F -FDG,⁵⁰ does not specifically localize within cancer cells, and can also demonstrate uptake in BPH. Despite promising results in a few studies (which are described elsewhere),⁵¹ no definitive conclusions for the use of acetate could be drawn owing to the limited number of patients involved in the studies. Given these observations, FDG and acetate are not commonly used. The most extensively studied radiotracer with the most encouraging results 'with regards to staging prostate cancer is choline, labelled with either ^{11}C or ^{18}F . The rationale for choline use is based on the fact that an increased number of high affinity choline transporters and increased activity of the enzyme choline kinase in prostate cancer cells are associated with a paralleled increase in choline, an essential component of cell membrane phospholipids.⁵² The main difference between ^{11}C -choline and ^{18}F -fluorocholine (^{18}F -FCH) is their half-lives (20 min for ^{11}C -choline compared with 110 min for ^{18}F -FCH), restricting the use of the former to centres with on-site cyclotrons. Otherwise, according to our knowledge, direct comparison of ^{11}C -choline-PET-CT and ^{18}F -FCH-PET-CT imaging in prostate cancer has not yet been conducted.

In terms of local staging of prostate cancer, PET-CT imaging with ^{11}C -choline and ^{18}F -FCH seem to have a greater role in restaging of patients with biochemical relapse after local treatment than in initial staging of untreated high-risk prostate cancer (Figure 4). According to a meta-analysis by Umbehrr and colleagues,⁵³ pooled results for restaging patients with prostate cancer reached the "high diagnostic evidence" criteria determined by the evidence-based medicine working group,⁵⁴ whereas those for initial staging did not. Other studies have demonstrated a similar trend in using ^{11}C -choline and ^{18}F -FCH in PET-CT for restaging compared with initial staging of prostate cancer.⁵⁵ However, in one study that used ^{18}F -FCH for initial staging of patients with high-risk disease, ^{18}F -FCH-PET-CT altered the management plan from curative intent to palliative care in 20% of the study cohort.⁵⁶ Another study demonstrated statistically significant correlation ($R = 0.68$, $P = 0.0001$) between foci of ^{18}F -FCH uptake on PET-CT and sextants with tumoral infiltration on histopathological analysis.⁵⁷ The ligand prostate-specific membrane antigen (PSMA) is a novel PET-CT radiotracer that is demonstrating potential according to several studies, such as increased focal uptake at the site of the biopsy-proven prostate cancer in 77% of the patients in one study.⁵⁸ Eiber *et al.*⁵⁹ conducted a study involving 248 patients with biochemical recurrence following radical prostatectomy and reported substantially higher cancer-detection rates when using ^{68}Ga -PSMA-PET-CT than when other imaging modalities were used, even in patients with low PSA levels (<0.5 ng/ml).⁵⁹ Currently, PSMA-PET-CT or any of the molecular imaging techniques have a minimal



Figure 2 | Assessment of extraprostatic extension on multiparametric MRI. Axial T2-weighted image shows decreased focal signal representing the patient's known tumour in the right posterior peripheral zone. An overlying asymmetric irregular capsular bulge consistent with extraprostatic extension is visible.

role in routine assessment of EPE and/or SVI in primary patients with high-risk prostate cancer. The literature for PSMA and other PET agents largely relates to recurrent disease, lymph nodes, and metastatic disease.

Current lymph node imaging modalities CT and MRI

Evaluation of patients for metastatic pelvic lymph nodes is most commonly performed using either CT or MRI. However, lymph node staging represents a challenge for all imaging modalities. Detection of metastatic lymph nodes is largely based on the measurement of nodal short-axis diameters, but this approach is recognized to be prone to both false-positive and false-negative interpretations. Thus, consideration of nodal morphology is also important. Nodal features that are suspicious for metastatic disease include a round shape rather than just an ovoid or elliptical shape, loss of the expected nodal fatty hilum, and irregular or poorly defined outer contours. Up to 12.5% of patients with Gleason score ≥ 8 prostate cancer will have lymphadenopathy detected by CT, while 22.9% will have pathological lymphadenopathy at the time of radical prostatectomy. The overall sensitivity, specificity, PPV, and NPV of detecting metastatic lymph node involvement by CT are 7%, 100%, 85%, and 100%, respectively. Thus, a normal CT does not rule out nodal disease.²⁴ Known rates of metastasis observed within lymph node dissection must be considered within the context of men with low enough risk to be considered candidates for surgery.

Detection of metastatic disease in lymph nodes by MRI is has similar limitations to detection by CT. As nodal size alone is a poor predictor of metastatic disease, lacking both sensitivity and specificity, past literature has provided variable size thresholds for identifying metastatic nodes. However, lack of agreement exists regarding the optimal threshold, and diagnostic accuracy remains

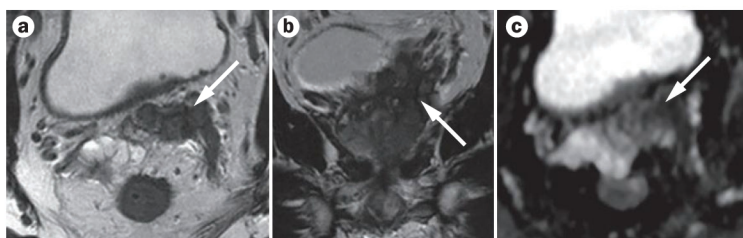


Figure 3 | Assessment of seminal vesicle involvement evaluated using multiparametric-MRI. **a** | MRI demonstrating seminal vesicle invasion in an axial T2-weighted image showing confluent mass-like decreased T2 signal throughout the left seminal vesicle, which was proven to represent seminal vesicle invasion. **b** | Coronal T2-weighted image showing direct extension of the left seminal vesicle abnormality from the tumour within the left base of the prostate. **c** | Axial apparent diffusion coefficient map showing markedly decreased apparent diffusion coefficient within the left seminal vesicle, consistent with seminal vesicle invasion.

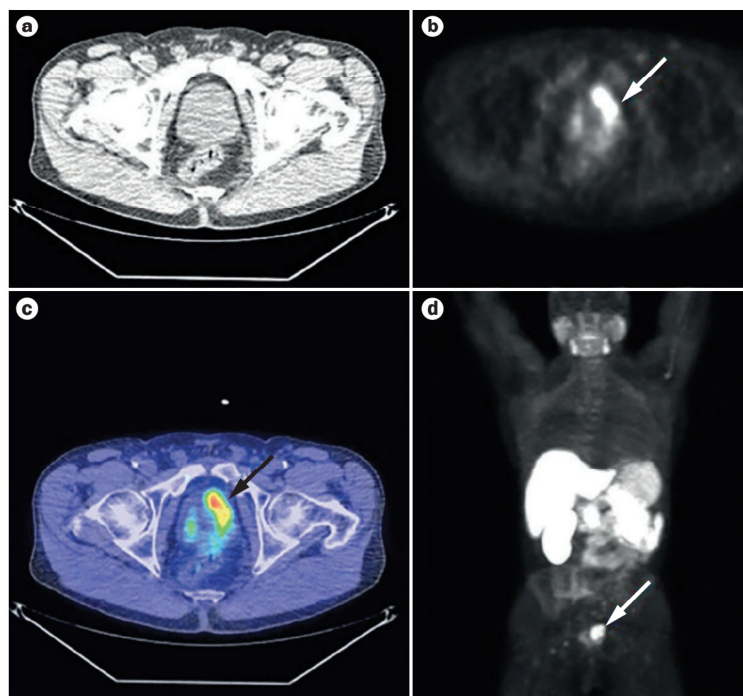


Figure 4 | ^{18}F -PET-CT for initial staging of prostate cancer in a newly diagnosed 70 year old with a serum PSA level of 73.6 ng/ml, demonstrating focal uptake in the left aspect of the prostate gland that is consistent with the primary tumour. **a** | Axial CT, **b** | PET, **c** | fusion PET-CT and **d** | maximum intensity projection. Abbreviation: PET, positron emission tomography. Images courtesy of Val Lowe, Professor of Radiology, Mayo Clinic, Minnesota.

limited at any threshold. Thus, lymph node size must be combined with node morphology. Morphological features such as elliptical versus round shape, lack of fatty hilum, and irregular margins assist in identifying lymph node involvement.

DWI could potentially improve assessment for metastatic lymph nodes using MRI, with metastatic nodes showing lower ADC values than benign nodes.⁶⁰ In addition, one study reported detection of metastatic disease in normal-sized nodes in some patients diagnosed as N0 on standard cross-sectional imaging.⁶¹ CT and MRI are largely considered interchangeable for nodal assessment,

as both generally rely on morphologic criteria for evaluation, and neither is sufficient, as they both have similar limitations. One imaging modality is not recommended over the other, as both remain suboptimal. Advanced novel MRI methods could improve the role of MRI in the future.

Positron-emission imaging

Despite the slightly better performance characteristics of PET-CT compared with CT or MRI reported in some studies and summarized elsewhere,⁶² most studies agree that both ^{11}C -choline-PET-CT and ^{18}F -FCH-PET-CT exhibit high specificity but low sensitivity in detecting lymph node metastases in patients with high-risk prostate cancer (Figure 5).^{63,64} A study by Haseebuddin *et al.*⁶⁵ reported slightly better sensitivity and specificity (68% and 78%, respectively) for ^{11}C -acetate-PET-CT in high-risk patients than sensitivities and specificities reported for ^{11}C -choline-PET-CT and ^{18}F -FCH-PET-CT.

The major limitation for all three imaging modalities is the size of metastatic lymph nodes, reported to be <4 mm in up to 45% of cases,⁶⁶ a size which is often below PET resolution. Thus, extended pelvic lymph node dissection remains the gold standard for detection of lymph node metastases. Ultimately, none of the preoperative imaging modalities currently available reaches clinically acceptable diagnostic accuracy for detection of lymph node metastases owing to the incidence of metastasis in normal-sized lymph nodes among men under consideration for therapy with curative intent. More studies are needed to further elucidate the role of choline-PET-CT and acetate-PET-CT in preoperative lymph node staging in patients with high-risk prostate cancer. Additional novel radiotracers labelled with ^{18}F are also being investigated to improve the accuracy of PET; these tracers include anti-1-amino-3- ^{18}F -fluorocyclobutane-1-carboxylic acid (anti- ^{18}F -FACBC, a synthetic L-leucine analogue),⁶⁷ and 2-(3-{1-carboxy-5-[(6- ^{18}F -fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid, (^{18}F -DCFPyL, a potential imaging agent for PSMA).⁶⁸

Current bone imaging modalities

Whole-body bone scintigraphy

The current standard imaging test for bone metastases is whole-body bone scintigraphy⁶⁹ for initial staging of prostate cancer, relapse in the setting of a rising PSA level,⁷⁰ or serially to monitor response to systemic therapy for patients with known metastatic disease.⁷¹ Metastases found by bone scintigraphy are detected in 2.3% of men with PSA levels <10 ng/ml, 5.3% of men with PSA levels 10.1–19.9 ng/ml, and 16.2% of men with PSA levels 20.0–49.9 ng/ml.²⁴ Detection rates are as high as 29.9% in men with Gleason score ≥ 8 prostate cancer.²⁴

Bone scintigraphy is usually performed using single photon scintigraphic imaging with the bone-seeking radiopharmaceutical $^{99\text{m}}\text{Tc}$ -methylene diphosphonate ($^{99\text{m}}\text{Tc}$ -MDP).⁷¹ In routine practice, this radiopharmaceutical is not typically used as a quantitative biomarker in the sense that a numerical value is not usually assigned

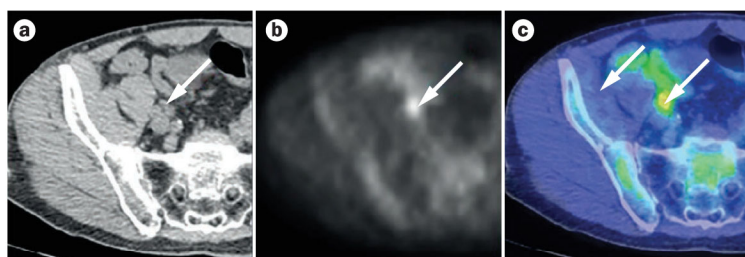


Figure 5 | Initial prostate cancer staging using ^{18}F -choline-PET-CT, demonstrating focal uptake within a 5 mm right external iliac lymph node (arrow), consistent with a nodal metastasis, in a 70-year-old patient with newly diagnosed prostate cancer and serum PSA level of 73.6 ng/ml. **a** | Axial CT, **b** | PET and **c** | fusion PET-CT. Abbreviation: PET, positron emission tomography. Images courtesy of Val Lowe, Professor of Radiology, Mayo Clinic, Minnesota.

to bone lesions to indicate disease severity. However, evidence exists that quantitative analysis with bone scintigraphy can be performed with the Bone Scan Index, which might be a reliable quantitative estimate of metastatic bone disease⁷² and has shown promise as a pharmacodynamic biomarker;^{73,74} however, the technique has been criticized as cumbersome to use⁶⁸ and has not been adopted in routine clinical practice.

Bone scintigraphy is a relatively sensitive modality for detecting osteoblastic bone metastases and is widely available and easy to perform;⁷⁵ however, it has a low specificity of 41%,⁷⁶ which is attributed to false-positive findings caused by benign conditions, such as healing fractures, degenerative or inflammatory joint disease, Paget disease, benign neoplasms, or metabolic disorders (for example hyperparathyroidism).^{77,78} Furthermore, bone scintigraphy is limited by an unclear relationship between bone-scan changes and disease progression or response to therapy.⁷¹ Some therapies such as androgen-deprivation therapy can cause tumour flare that presents as an increase in radiotracer uptake in metastatic bone lesions despite significant tumour cell death and clinical treatment response.⁷⁹ Bone scintigraphy also has low spatial resolution, and bone metastases can remain undetected, particularly at the early stage of disease when a lesion has low metabolic activity or is purely lytic.⁸⁰ CT is typically performed in conjunction with bone scintigraphy to look for extraosseous disease and can be used to correlate bone lesions with bone scintigraphy, in order to look for a sclerotic and/or lytic focus to confirm suspected metastases. In patients with an equivocal bone scintigraphy, the addition of single photon emission CT (SPECT) has been shown to improve diagnostic confidence and considerably reduce equivocal study reports.⁷⁷ SPECT also improves the sensitivity and the specificity of planar bone scans, especially in the evaluation of spine lesions.⁷⁸ Calculation of SUVs as a quantitative assessment of SPECT-CT is possible, similar to SUV measurement in PET-CT. However, quantitative assessment of SPECT-CT bone scintigraphy has not been widely investigated. In one study, Cachovan *et al.*⁸¹ demonstrated a strong correlation between SUV and bone CT density in lumbar vertebrae of healthy patients, but concluded that further

investigation was needed before potential use for following osseous metastases under therapy. Currently, this quantitative approach to SPECT-CT has not been approved for routine clinical use and, accordingly, is not widely applied in practice.

Sodium fluoride-18

Bone-seeking radiopharmaceuticals used with PET—such as ^{18}F -sodium fluoride (^{18}F -NaF)—coupled with CT images in a hybrid PET-CT examination, promise to provide highly sensitive 3D anatomical and functional imaging of the skeleton (Figure 6).⁸⁰ Compared with $^{99\text{mTc}}$ -MDP, ^{18}F -NaF has twofold higher bone uptake, faster blood clearance, and a higher target:background ratio.^{82–84} ^{18}F -NaF uptake is an indirect measurement of tumour activity, reflecting the metabolic response of bone tissue to the presence of metastases. Studies have shown that ^{18}F -NaF-PET-CT has a significantly higher sensitivity than planar-CT and SPECT bone scintigraphy for the detection of skeletal metastases in prostate cancer.⁶⁹ Compared with bone scintigraphy, ^{18}F -NaF-PET-CT has a higher specificity leading to its higher accuracy.⁷¹ Despite the reported oversensitivity of ^{18}F -NaF-PET-CT compared with bone scan, which could compromise specificity, we feel that the greatly improved localization of foci with increased uptake provided by the CT portion of the ^{18}F -NaF-PET-CT compared with bone scan leads to improved diagnostic accuracy. In addition, the use of ^{18}F -NaF-PET-CT avoids the need for an additional SPECT or SPECT-CT in equivocal planar bone scans, and, therefore, could also decrease patient anxiety.¹⁸ ^{18}F -NaF has been recommended as a second bone-seeking agent to enhance diagnostic sensitivity for skeletal metastases in patients who have prostate cancer.⁸⁵ However, ^{18}F -NaF-PET-CT is not widely available for clinical routine use at all centres.

MRI

The use of MRI for bone imaging in prostate cancer includes the use of quantitative functional parameters measured by advanced MRI techniques, such as DCE and DWI.⁸⁶ DCE-MRI can detect changes to blood flow in bone tissue and use these changes to identify marrow infiltration by prostate cancer.⁸⁷

DWI can detect metastases,^{88–90} and has been shown to be useful as a predictive imaging modality in the detection of treatment response.^{91–93} DWI has improved diagnostic sensitivity compared with conventional anatomical MRI,⁹⁴ and enables calculation of the tissue ADC, a quantitative measure of tissue diffusivity typically using ≥ 2 diffusion sensitizing gradients, which are referred to as 'b values'. Several studies have demonstrated a significant negative correlation between ADC and SUV on ^{18}F -FDG-PET, indicating the utility of these parameters for tumour surveillance in many different non-osseous malignancies.^{95–100} DWI has also been shown to be useful for quantitatively assessing the response of prostate cancer bone metastases to systemic therapy with antiandrogens.⁹²

Molecular imaging of metastatic disease

¹⁸F-fluorodeoxyglucose

¹⁸F-FDG-PET has been demonstrated to target extra-osseous and osseous metastases in castration-resistant prostate cancer (CRPC).¹⁰¹ This technique has also demonstrated utility for tumour surveillance, with one study indicating that improvement on ¹⁸F-FDG-PET-CT was concordant with a decrease in PSA levels.¹⁰² CRPC might have increased metabolic activity (with a higher glucose metabolism than castration-sensitive prostate cancer), making ¹⁸F-FDG a particularly useful radiotracer for the identification of a castration-resistant phenotype, as well as being a pharmacodynamic biomarker.⁷¹ Nevertheless, the role of ¹⁸F-FDG-PET in patients with treatment-naïve prostate cancer is still debated given that lower sensitivities than bone scan have been reported when imaging well-differentiated prostate cancer, which might be secondary to the low glucose metabolism of bone metastases in treatment-naïve patients.^{69,103} Generally, ¹⁸F-FDG-PET has a limited role in the primary diagnosis and staging of prostate cancer, as tracer accumulation overlaps in normal and abnormal prostate tissues.¹⁰⁴

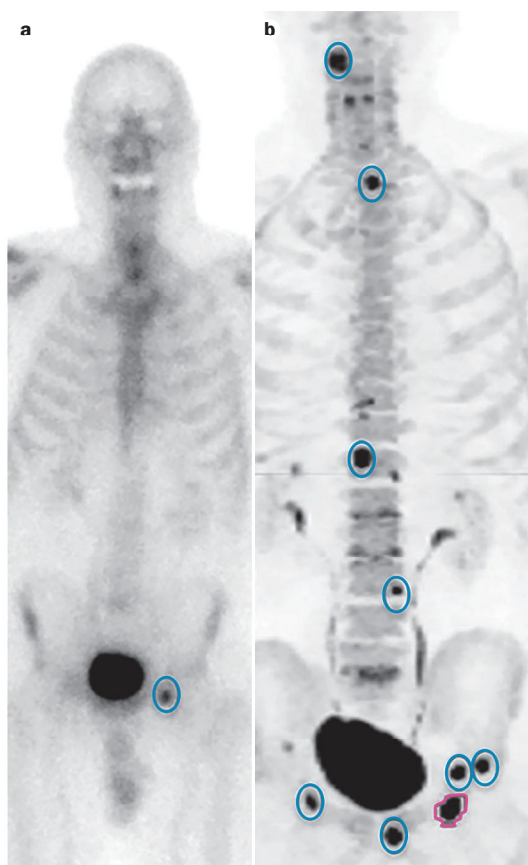


Figure 6 | Initial staging workup showing metastatic disease to bone in an 85-year-old patient with a *de novo* non-CRPC diagnosis. **a** | Bone scan demonstrates one metastatic lesion in left acetabulum. **b** | ¹⁸F-NaF-PET-MRI (performed 3 weeks later) shows nine metastatic lesions, demonstrating the higher sensitivity of PET-MRI. Abbreviations: CRPC, castration-resistant prostate cancer; PET, positron emission tomography.

¹¹C-choline

The use of radiolabelled choline for PET-CT imaging, originally performed using ¹¹C, has shown utility in the identification of prostate cancer.^{105,106} Unlike ¹⁸F-FDG, which is particularly useful for identifying the metabolically active castration-resistant phenotype, radiolabelled choline has been noted to be useful in detecting metastases in treatment-naïve patients as well as patients with CRPC, with no current evidence for these two types of cancer having different, phenotype-specific metabolism.⁷¹ Normal cell membrane integrity depends on choline for the production of phosphatidylcholine. Cancer-cell membranes have elevated phosphatidylcholine levels, resulting in increased amounts of trapped choline in tumour-cell membranes.¹⁰⁵ Although radiolabelled choline has shown utility in the identification of bone metastases, bone scan was shown to have a higher overall accuracy in one study;¹⁰⁶ therefore, this modality is not recommended as a substitute for bone scan.⁷¹ Furthermore, ¹¹C has a short (20 min) half-life, which precludes centralized production and distribution of the radiopharmaceutical in most centres that do not have a cyclotron.⁷¹ The requirement for an onsite cyclotron ensues further operational challenges, including the need for specially adapted onsite chemical synthesis apparatus to produce the radiopharmaceuticals after radioisotope preparation.

¹⁸F-fluorocholine

¹⁸F-FCH is a positron-emitting nuclide that is used in PET imaging. In contrast to ¹¹C, which has a short, 20-minute half-life, ¹⁸F has a longer half-life of approximately 2 h, potentially making it more readily available for clinical use.⁷¹ ¹⁸F-fluorocholine has shown promise in the detection of recurrent and metastatic prostate cancer.¹⁰⁷ Furthermore, ¹⁸F-fluorocholine-PET-CT has demonstrated a higher accuracy than ¹⁸F-NaF-PET in identification of bone metastases in CRPC.¹⁰⁸ In a comparison with radical prostatectomy with extended pelvic lymphadenectomy, ¹⁸F-fluorocholine-PET-CT demonstrated a sensitivity and PPV specificity of 56% and 98%, respectively, for detecting lymph node involvement and 78% and 94%, respectively, on a patient-based analysis.¹⁰⁹ ¹⁸F-fluorocholine accumulates in the bladder (similar to ¹⁸F-FDG), which can obscure the prostate, whereas ¹¹C-choline does not show bladder accumulation in most cases. Furthermore, of these agents, only ¹¹C-choline has been FDA approved for evaluation of suspected recurrent and metastatic prostate cancer and noninformative bone scintigraphy, CT, or MRI.¹¹⁰

¹¹C-acetate

The fatty acid acetate has been radiolabelled with ¹¹C and studied for its ability to detect prostate cancer.^{111,112} Acetate is a metabolite that is transported across the cell membrane via the monocarboxylate transporter. The major acetate consumers are the Krebs cycle and the metabolic pathways that are related to the production of phospholipids, which are facilitated by the fatty acid synthase reaction. The basis of the increased ¹¹C-acetate



Figure 7 | Differentiating metastatic lesions from benign lesions on ^{18}F -NaF-PET-MRI. **a** | PET and DWI. **b** | ADC. **c** | Combined PET-ADC. Metastatic lesions show increased uptake ^{18}F -NaF on PET and restricted diffusion on DWI and ADC (circles). Abbreviations: ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; PET, positron emission tomography.

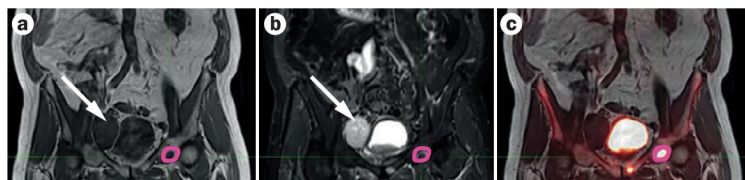


Figure 8 | Differentiating metastatic lesions from benign lesions on ^{18}F -NaF-PET-MRI. **a** | T1WI. **b** | T2-STIR-MRI. **c** | Combined PET-T1. Metastatic bone lesions show increased ^{18}F -NaF uptake on PET, have dark signal on T1WI, and bright signal on T2W-STIR (circles) and prostate gland enlargement with a prostate cancer mass shows a large right internal iliac metastatic lymph node (arrows). Abbreviations: PET, positron emission tomography; STIR, short tau inversion recovery; T1WI, T1-weighted image; T2W, T2-weighted.

uptake in prostate cancer stems from the malignancy-induced upregulation of fatty acid synthase. Studies have shown that ^{11}C -acetate has a high accuracy in detection and determining response to treatment in prostate cancer metastases.^{65,113–115} Notably, ^{11}C -acetate does not show bladder accumulation in most patients.

Prostate-specific membrane antigen

PSMA is a transmembrane protein expressed in all types of prostatic tissue, and exhibits increased expression in prostate cancer.¹¹⁶ The PSMA gene is located on the short arm of chromosome 11 in a region that is not commonly deleted in prostate cancer.¹¹⁷ PSMA has known enzymatic activities and acts as a glutamate-preferring carboxypeptidase, although the influence of these enzymatic functions on human prostate tissue remains unclear. Radioimmunoconjugate forms of anti-PSMA monoclonal antibodies are being studied in prostate cancer imaging.⁷¹ PSMA was originally radio-labelled with ^{111}In linked via a chelate (pendetide) to the murine monoclonal antibody capromab. ^{111}In -labelled capromab pendentide is approved by the FDA for the identification of recurrent prostate cancer after primary definitive therapy.¹¹⁸ However, this modality has limitations including low sensitivity for bone metastases as well as nonspecific binding in blood pool structures, which can lead to problematic evaluation of lymph nodes lying in close proximity to the vessels. Such issues can lower diagnostic accuracy and have considerably limited this modality's use.¹¹⁹ Some studies suggest that accuracy of detection of prostate cancer might improve with the use of a ^{89}Zr -labelled anti-PSMA antibody and PET,^{120,121} rather than ^{111}In , which uses SPECT and has a lower sensitivity than PET. In 2014, analysis of ^{68}Ga -PSMA-ligand PET-CT demonstrated a sensitivity,

specificity, NPV and PPV of 76.6%, 100%, 91.4%, and 100%, respectively, when assessing recurrent prostate cancer lesions.¹²²

PET-MRI

Hybrid PET-MRI based on simultaneous PET and MRI acquisition was approved for human use by the FDA in 2011. This technology is capable of providing whole-body assessment of tumour burden in oncology patients. Advanced imaging during PET-MRI through the use of PET and DWI enables the evaluation of biological properties such as tumour metabolism and cellularity, respectively. Anatomical imaging during PET-MRI is important for assessing tumour size and morphology, which is best evaluated using conventional MRI sequences such as T1-weighted imaging (T1WI), T2WI, and short tau inversion recovery (STIR)-MRI, as these sequences have better spatial resolution and anatomical detail than DWI-MRI. PET and MRI performed separately have been shown to be complementary modalities for detecting bone metastases.¹²³ Mosavi and colleagues¹²⁴ compared whole-body DWI and ^{18}F -NaF-PET-CT in 49 patients with high-risk prostate cancer, demonstrating that DWI had a higher specificity but lower sensitivity than ^{18}F -NaF-PET-CT for detection of osseous metastases. However, this study did not incorporate PET-DWI using hybrid PET-MRI, but rather compared DWI-MRI with ^{18}F -NaF-PET-CT. The combination of the high sensitivity of ^{18}F -NaF-PET with the superior specificity of DWI-MRI into one imaging study, with the ability to fuse PET and MRI images together, might achieve a highly accurate hybrid imaging modality (Figure 6). One study demonstrated that ADC maps generated from DWI can reliably differentiate marrow replacement from metastatic disease and benign processes such as traumatic or osteoporotic vertebral fractures.¹²⁵ Thus, the combination of ADC maps with PET information through PET-MRI has great promise in problem solving for cases in which bone scintigraphy and PET-CT are inconclusive (Figure 7). PET-MRI shows promise in detecting bone metastases caused by prostate cancer and in tumour surveillance to assess treatment response (Figure 8). A study evaluating bone metastases from prostate cancer with simultaneous ^{18}F -choline-PET-MRI using combined SUV and ADC metrics demonstrated a moderate but significant inverse correlation between increased choline metabolism and ADC values of bone metastases from prostate cancer.¹²⁶ Further investigation of a multimodality approach using simultaneous PET-MRI in bone metastasis of prostate cancer appears justified. The major limitations of this modality currently are limited accessibility and high economic costs.

Clinical implications

Careful selection of patients for the appropriate imaging tests is essential and relies on knowledge of the strengths and limitations of each study. mpMRI of the prostate has been shown to influence the decision to preserve or resect neurovascular bundles during radical prostatectomy.^{47,48} Furthermore, mpMRI of the prostate might have a role in

detection of local recurrence, influencing management decisions for salvage therapy.¹²⁷ In men who present with PSA relapse after treatment, ¹⁸F-FDG-PET might be useful in detecting recurrence and directing appropriate treatment, such as salvage radiation therapy for local recurrence in the prostate bed or systemic therapy for metastatic disease.¹²⁸ ¹⁸F-choline-PET-CT has been employed to detect occult disease and differentiate localized from systemic disease recurrence, subsequently guiding an optimal treatment approach such as initiation of androgen deprivation therapy.¹²⁹

The benefits of imaging must ultimately be weighed against potential risks and harms, which have been described in detail elsewhere.^{130–132} Technical innovations have contributed to lowering the radiation dose from imaging, but the lifetime attributable risk of cancer from radiation exposure remains a concern.¹³³ Examinations should be clinically justified, and measures should be taken to reduce the dose. Awareness and communication of potential radiation-induced health risks from medical imaging remain paramount.¹³⁴

Conclusions

Imaging in high-risk prostate cancer still predominantly relies on radionuclide bone scan, CT, and MRI. Novel imaging techniques and radiopharmaceuticals combined with mpMRI and PET-CT are currently being investigated and incorporated into clinical use; these more advanced approaches offer improved sensitivity and specificity and, therefore, enable more accurate assessment of disease. These emerging techniques could also enable better prediction and assessment of treatment response using quantitative parameters. In the future, integrated PET-MRI could provide a single, comprehensive assessment of local disease extent, lymph nodes, and bones, as well as functional assessment of tumour aggressiveness and prognosis. Nevertheless, the development of new accurate imaging has many obstacles that need to be considered, including economic costs, accessibility, and technical limitations. Continued studies are warranted to further establish the role of these new modalities in the management of patients with high-risk prostate cancer.

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Author contributions

All authors made substantial contributions to discussion of article content, writing, reviewing, and editing the article before submission. M.A.B., A.B.R., L.S.B. and R.A.R. researched data for the article.