NEW ADVANCES IN DIAGNOSIS AND RADIOLOGIC FOLLOW UP OF METASTATIC PROSTATE CANCER

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14 DECEMBER, 2023

Prostate Cancer

General information

Prostate cancer is the most common solid cancer in men worldwide. Owing to the typically long course of the disease, the prevalence of metastatic prostate cancer is increasing.

The biology and clinical course of prostate cancer are highly variable, ranging from indolent localized disease to highly aggressive widely disseminated disease.

Adenocarcinoma is the most common histologic type.

Screening

Screening has been done with a PSA test and digital rectal examination. If the tests suggest an increased likelihood of prostate cancer (PSA ≥4.0 ng/mL or abnormal DRE), prostate biopsy is usually indicated.

New studies with screening through imaging methods are discussed.

Prostate Cancer

Prostate Biopsy (Histologic Diagnosis)

Systematic biopsy

10-12 cores are randomly obtained from the prostate, guided by TRUS.

MRI-targeted biopsy

After identifying areas of interest at MRI, the images are merged with the real-time TRUS images, allowing targeted biopsies to specific lesions.

In-bore MRI-guided biopsy

Enables a visual MRI-controlled sample acquisition with needle-in documentation for patients with previous negative systematic biopsy results and positive MRI findings. It allows even small lesions to be sampled and helps detect more clinically significant cancer and less clinically insignificant cancer than systematic biopsy, although it is more costly, more time-consuming, and less available.

Prostate Cancer

Treatment

Treatments include external radiation therapy (in some cases, combined with brachytherapy to increase the radiation dose to the primary tumor) with androgen deprivation therapy and radical prostatectomy combined with extensive pelvic lymph node dissection.

Follow-up

After treatment, monitoring of PSA levels is important to determine if any disease was not resected and if additional therapy is indicated:

- Undetectable PSA: continue to monitor serum PSA level
- PSA does not go undetectable or increases its serum levels: residual disease or biochemical recurrence is presumed. Evaluate for metastatic disease and determine therapy and subsequent therapy

Prostate Cancer

Active Surveillance

Patients with low-risk, low-grade (Gleason 6), slow-growing tumors confined to the prostate gland may consider monitoring of prostate cancer in its localized stage until further treatment is needed to halt the disease at a curable stage. These patients may be followed with periodic evaluations with PSA, DRE, prostate biopsy, and imaging examinations.

Biochemical Recurrence

Biochemical recurrence is an increase in PSA levels in patients who have had treatment with a curative purpose for localized disease, in the absence of clinical or radiologic signs of recurrence.

Most accepted cutoffs: PSA level >0.2 ng/mL across two measures (and rising) after radical prostatectomy or PSA level ≥than 2.0 ng/mL above the nadir after radiation therapy

PSA level recurrence after prostatectomy occurs in 20%–35% of cases, with a median time to biochemical recurrence of 2–3 years after surgery

BIOCHEMICAL RECURRENCE

The median time to development of distant metastasis after PSA level recurrence without any treatment is approximately 8 years, so the decision to treat and the optimal treatment must be individualized.

For patients with biochemical recurrence, it is of great clinical importance in guiding management to determine if there is local recurrence, distant metastasis, or a combination of these

Imaging is generally considered in the clinical context of recurrent or rising level of serum prostate-specific antigen (PSA) after treatment.

Conventional imaging modalities: abdominopelvic CT and bone scanning.

advanced imaging modalities: Multiparametric MRI of the treated prostate or prostatectomy bed for local recurrence

prostate-specific molecular PET such as with carbon 11 (11C) choline or fluorine 18 (18F) fluciclovine for metastatic disease

Methods

- TRUS
- CT
- BS
- MRI
- PET

- ^{18}F-FDG
- ^{18}F-NaF
- ^{11}C-Chol
- ^{18}F-Chol
- ^{18}F-FACBC
- ^{68}Ga-PSMA
- ^{18}F-PSMA

Table 1: Disease States and Definitions of Prostate Cancer Recurrence and Metastasis

Disease State	Definition
Biochemical failure (or relapse)	Rise in PSA level without symptoms after definitive curative-intent therapy
After radical prostatectomy	Undetectable PSA level with *(a)* two or more subsequent PSA level increases or *(b)* two PSA level measurements >0.2 ng/mL (NCCN and EAU guidelines)
After radiation therapy	PSA level ≥2.0 ng/mL above nadir (ASTRO Phoenix criteria)
After ablation	PSA level ≥2.0 ng/mL above nadir (adopted from ASTRO Phoenix criteria)
Castration (or hormone)–sensitive (or naive) prostate cancer (CSPC)	Patient not receiving ADT at time of progression
Metastatic	Patient with metastasis
Nonmetastatic	Patient without metastasis
Castration (or hormone)–resistant prostate cancer (CRPC)	Disease progression despite ADT and castrate level of serum testosterone (<50 ng/dL [<1.7 nmol/L])
Metastatic	Patient with metastasis
Nonmetastatic (M0)	Patient without metastasis
Metastatic disease	
Oligometastatic	Limited number (eg, three or fewer) of clinically detectable bone or soft-tissue metastases, which may be amenable to local treatment with curative intent
Systemic	Clinically documented multiple metastatic disease, which requires systemic therapy

Note.—ADT = androgen-deprivation therapy, ASTRO = American Society for Radiation Oncology, EAU = European Association of Urology, NCCN = National Comprehensive Cancer Network.

CONVENTIONAL IMAGING

- ***Bone Scanning.*—**Whole-body bone scanning with technetium 99m (99mTc)–labeled methylene diphosphonate (MDP) is readily available and traditionally has been used for evaluation of patients with metastatic prostate cancer.

Bone imaging		
Bone scanning (technetium 99m [99mTc]–labeled methylene diphosphonate [MDP])	Widely available Whole-body imaging Useful for detecting osteoblastic metastasis Commonly used for posttreatment follow-up	Osteolytic metastasis can lead to false-negative diagnosis Bone scan flare response Poor spatial resolution Radiation exposure When results are inconclusive, additional imaging (skeletal radiography, CT, MRI, or ^{18}F–sodium fluoride PET/CT) is required
^{18}F–sodium fluoride PET/CT	Superior sensitivity to that of conventional bone scanning Faster acquisition time than conventional bone scanning	Not reimbursed by Medicare Not tumor specific Flare response phenomenon

- Increased uptake of tracer reflects bone turnover, which may be caused by metastatic prostate cancer or benign conditions (eg, fracture, degenerative changes, Paget disease).

- When results of bone scanning are inconclusive for metastasis, skeletal radiography, CT, MRI, 18F–sodium fluoride PET/CT, or image-guided percutaneous needle biopsy may be performed for further characterization.
- PSA Best Practice Statement of the American Urological Association (AUA): states that routine use of bone scanning in the setting of biochemical recurrence is not justified in patients with a PSA level doubling time greater than 6 months and a PSA level less than 10 ng/mL. The guidelines of the American Society for Radiation Oncology (ASTRO) and AUA note that because most men with biochemical recurrence present with a PSA level less than 1 ng/mL, the potential yield of bone scanning for evaluation of biochemical recurrence would be low.

ABDOMINOPELVIC CT OR MRI AND CHEST IMAGING

Soft-tissue imaging		
CT	Widely available Useful for detecting bone involvement and nodal staging	Poor soft-tissue contrast of prostate and periprostatic soft-tissue structure as well as prostatic fossa after radical prostatectomy Radiation exposure
MRI of abdomen or pelvis	Excellent tissue contrast Allows functional imaging No radiation exposure	Morphologic and functional changes after primary therapy may decrease diagnostic performance Expensive Susceptible to artifacts

- readily available to evaluate soft tissue (lymph nodes and visceral organs) and bone.
- CT is not useful for detecting recurrent tumor in the surgical bed and has poor sensitivity for nodal metastases from prostate cancer, since large numbers of metastatic nodes are known to be normal-sized, although CT is useful in following response of known enlarged metastatic lymphadenopathy to treatment and guiding percutaneous needle biopsy
- CT is useful in detecting sclerotic bone and visceral metastases, although bone scanning and MRI are superior in diagnosis and follow-up of bone metastases.
- Chest radiography or CT is performed to assess for metastatic involvement in the lung, pleura, mediastinum, and bone.

- BS is highly sensitive but usually has low specificity. It is more sensitive than plain film and CT scans; however, MRI is superior for the evaluation of vertebral metastases.
- Although plain radiographs are highly specific, they have low sensitivity (44–50%). Because of limited contrast, medullary lesions are more difficult to detect in trabecular bone than in cortical bone
- The sensitivity of CT for the diagnosis of bone metastases ranges from 71 to 100%. Bone destruction and sclerotic deposits are usually clearly shown, and any soft tissue extension of bone metastases can be easily visualized. However, the ability to detect inter-trabecular spread remains controversial
- 18F FDG-PET detects the presence of bone metastases by directly quantifying metabolic activity
- MRI provides good contrast resolution of bone and soft tissue and therefore has good sensitivity and specificity for the detection for bone metastases. However, limited field of view and long examination time pose problems, which existed even before the development of WB-MRI

PROSTATE MULTIPARAMETRIC MRI

Table 2: Advantages and Disadvantages of Current Imaging Techniques for Prostate Cancer Recurrence

Imaging Modality by Type	Indications and Advantages	Disadvantages
Posttreatment imaging of prostate or prostatic fossa*		
Transrectal US	Used mostly for guiding prostate biopsy for tissue characterization	Limited tissue contrast between cancerous and benign tissue Cancer restaging is difficult
Multiparametric MRI	Indicated in biochemical recurrence after radiation treatment Used to guide targeted biopsy in irradiated prostate using MRI/US fusion software and in suspected locally recurrent tumor after prostatectomy	Morphologic and functional changes after primary therapy may decrease diagnostic performance Susceptible to artifacts Expensive Not portable

- Multiparametric MRI with small field of view of the treated prostate or prostatic fossa consists of morphologic T2-weighted imaging and functional imaging, including DWI and DCE imaging.
- The recently published Prostate Imaging Reporting and Data System (PIRADS) update to version 2.1 does not apply to posttreatment prostate cancer imaging, although the technical standards of high-quality multiparametric MRI in the cancer screening or detection setting governed by PIRADS are similar to what can be employed for posttreatment evaluation. Dynamic contrast-enhanced imaging in this setting is of much greater importance.

WHOLE-BODY MULTIPARAMETRIC MRI

- Addition of diffusion-weighted imaging with background body signal suppression (DWIBS) to whole-body MRI allows assessment for bone and soft-tissue metastasis.
- Whole-body MRI allows direct visualization of metastatic lesions with good sensitivity for bone metastases, without radiation exposure or use of intravenous gadolinium-based contrast agents.
- Recently, a scoring system—Metastasis Reporting and Data System for Prostate Cancer (MET-RADSP)—using whole-body MRI was proposed for comprehensive assessment of prostate cancer metastasis. However, in the United States, no established *Current Procedural Terminology* (CPT) codes are available for reimbursement

- Significant advantages of (WB-MRI) for detecting bone metastases:

❑ Evaluation can be performed with a single scan, which is potentially more cost-effective and time-saving for whole-body evaluations.

❑ it can be used for whole-body evaluation and treatment response monitoring.

❑ In particular, diffusion-weighted imaging (DWI) has become available for whole-body scanning, which has now been incorporated into the main sequence of WB-MRI

- Bone metastases are commonly found in the spine, pelvis, shoulder, and distal femur.
- These bone lesions can cause serious complications, such as spinal cord and nerve root compression, pathological fracture, and hypercalcemia .
- In adults, the axial skeleton contains red marrow.
- Batson showed that venous blood from the breast and pelvis flowed not only into the vena cava but also into the vertebral venous plexus, which extends from the pelvis to throughout the epidural and peri-vertebral veins

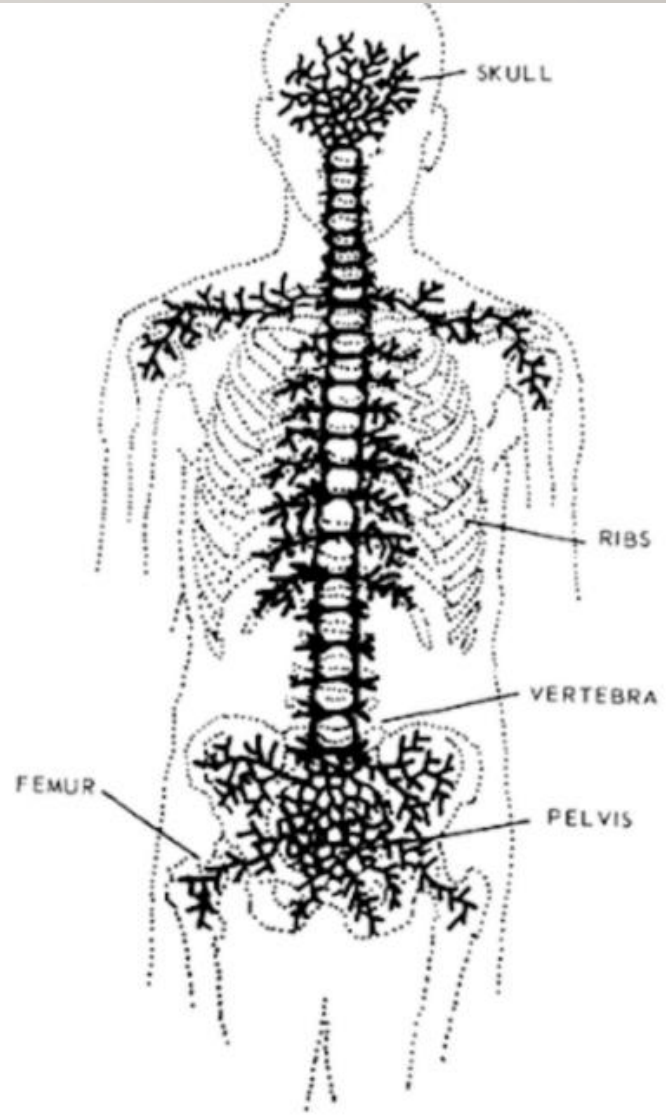
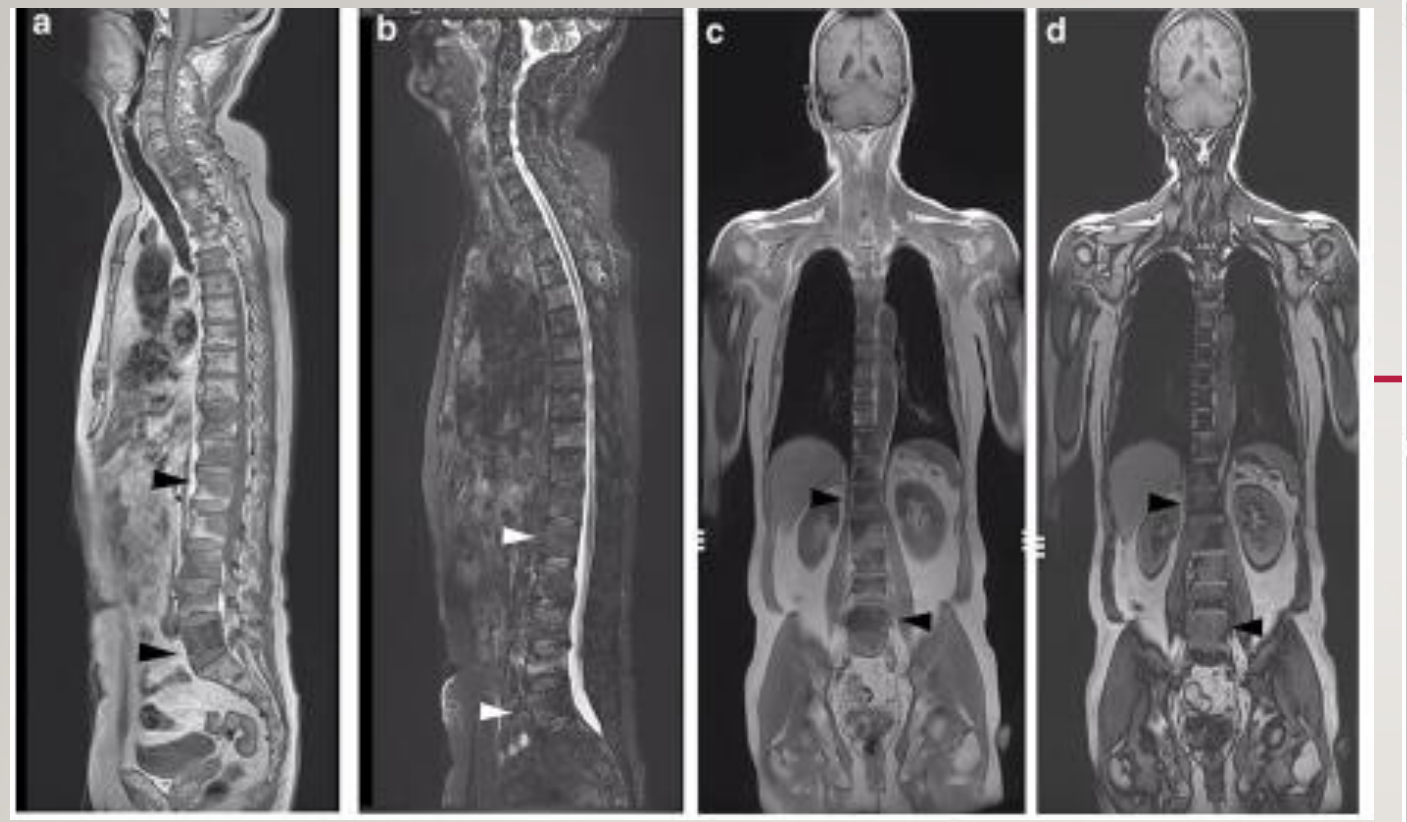
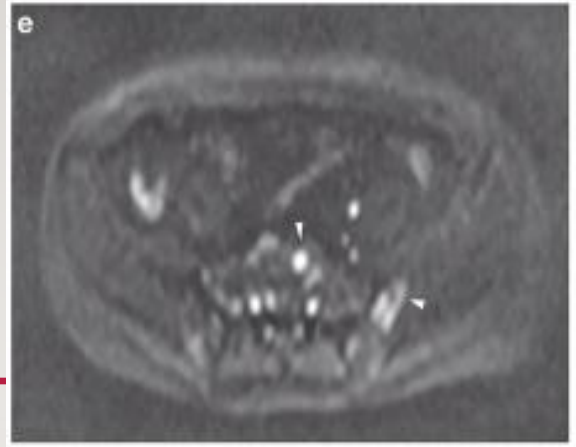


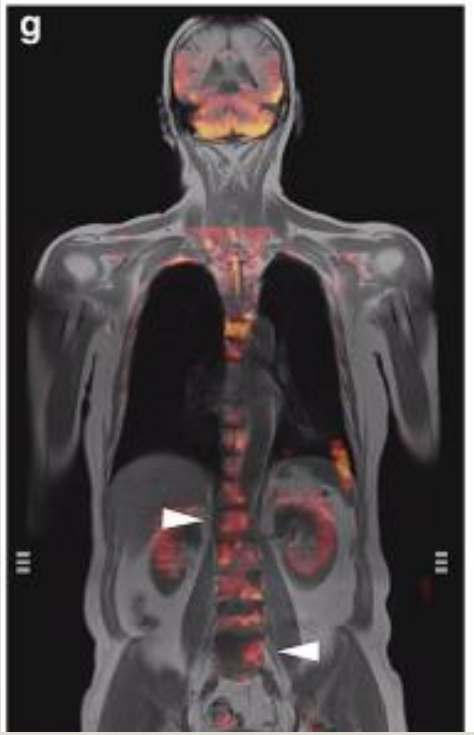
Fig. 1 Batson's venous plexus. Cited from *Diseases of the Spine and Spinal Cord* (Thomas N Byrne et al. P169, Oxford University Press)

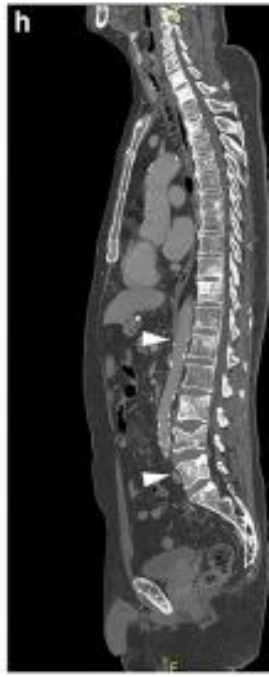
- Conventional classifications categorize bone metastases as osteoblastic, osteolytic and mixed types.
- This classification is based on the primary mechanism of interference with normal bone remodeling and the uptake of radiotracers, which depends on the quantity of the calcification of the metastases and osteoblastic activity. However, the recently identified inter-trabecular-type metastasis, which infiltrates the marrow space without altering the trabecular bone and is not radiologically visible but detectable on MRI, requires further characterization.
- Imaging modalities for diagnosing bone metastases include technetium-99 m bone scintigraphy (BS), plain radiography, computed tomography (CT), MRI, and 18F fluorodeoxyglucose (FDG)–positron emission tomography(PET)

since the development of WB-MRI, the basis for diagnosing bone metastases from prostate cancer has changed.

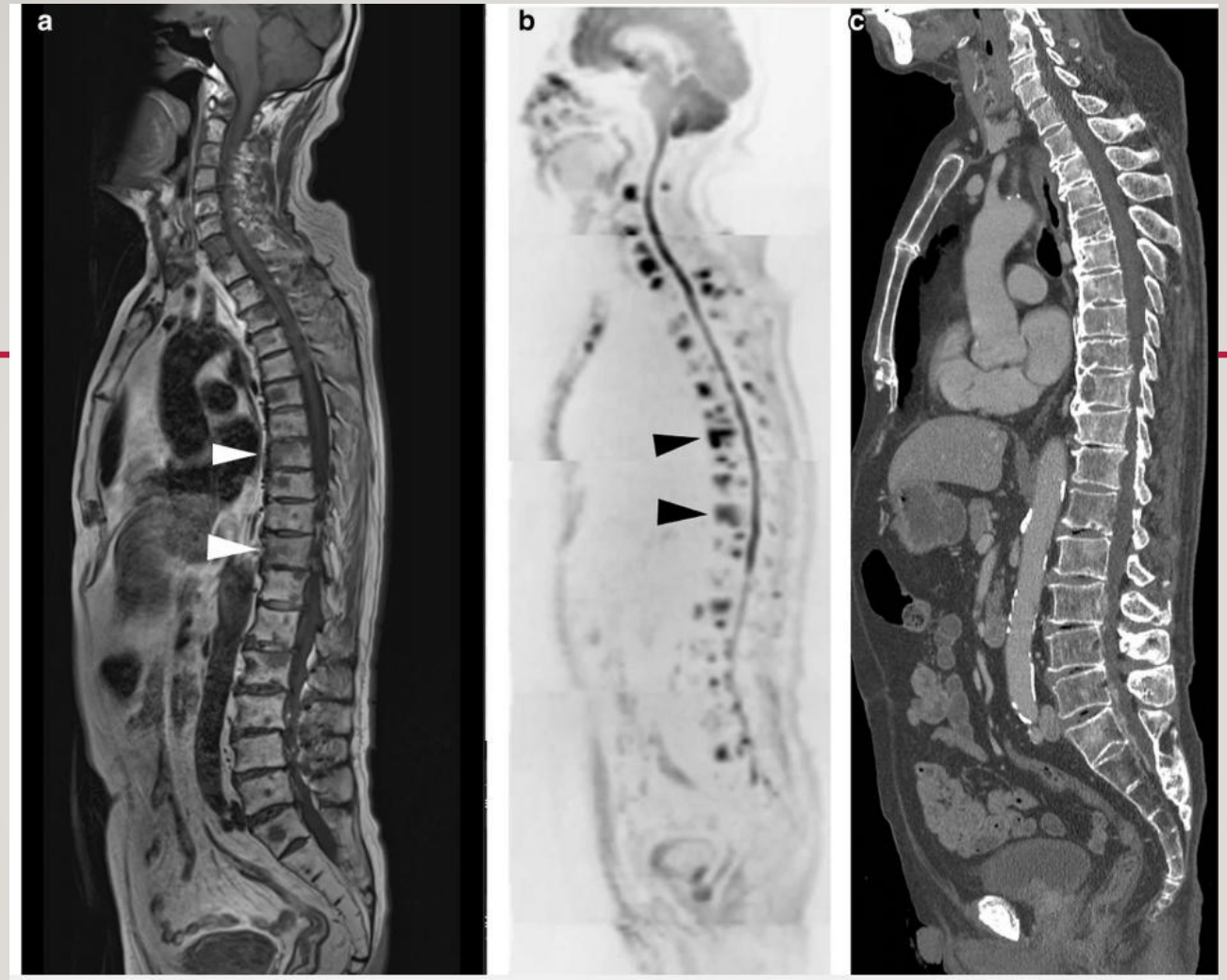








A a 69-year-old man with multiple bone metastases from prostate cancer. Serum PSA was 4.894 ng/mL.
a Total spine T1W image. **b** Total spine STIR image.**c** Body coronal in-phase T1W image.**d** Body coronal out-of-phase T1W image.
e Axial *b*= 1000 of the DW image at the level of the pelvic bone. **f** Coronal reconstructed DW image. This image is displayed as a black-and-white inverted image.
g Fused image combining in-phase coronal T1W image with coronal reconstructed DW imag.
.**h** Sagittal reconstruction of the CT image.
The diagnosis was osteoblastic metastases



Mixed-type/intertrabecular metastases. A 78-year-old man with a 4-year history of prostate cancer and transition to castration resistant prostate cancer (CRPC). Serum PSA was 5.954 ng/mL.
On the CT reconstructed sagittal image, obvious sclerotic or lytic changes were not observed. In fact, the diagnosis of multiple bone metastases using only CT examination was not possible. These CT findings were defined as intertrabecular metastases

- the oldest reports that included the term "*whole-body* MRI" date back to 1997. Since the beginning in the twenty-first century, various devices have been developed to enable a whole-body scan in a single session without the need to change the directions of the body, which include multichannel coil and tabletop extenders

Fig. 5 Multichannel coil: 20-channel head coil, 32-channel spine coil, and two or three 18-channel body-array coils were combined to cover the area of Batson's venous plexus, which is an area with a predilection for bone metastases

WB-MRI OR BS ?

- However, in 2020, Sun et al. performed a database search to conduct a meta-analysis to compare the diagnostic performance between WB-MRI and BS for the detection of bone metastases. The results showed that WB-MRI had higher but comparable patient-based specificity as BS (99% vs. 95%) but markedly higher sensitivity (94% vs. 80%). The authors concluded that WB-MRI has higher sensitivity and diagnostic accuracy than did BS and may be used for both the confirmation and exclusion of metastatic bone disease
- With the increase in the number of treatment options and improvements in patient survival, the use of WB-MRI for providing accurate diagnosis and therapy monitoring has become crucial

- Numerous investigators have subcategorised the metastatic state in APC

- by tissue involvement (bone/lymph nodes/visceral),
- by skeletal location (axial/peripheral),
- by number of lesions (oligometastatic or polymetastatic),
- and by the overall burden/volume of disease, because these have been shown to have prognostic and therapeutic value

CORE – CORE PLUS WB-MRI

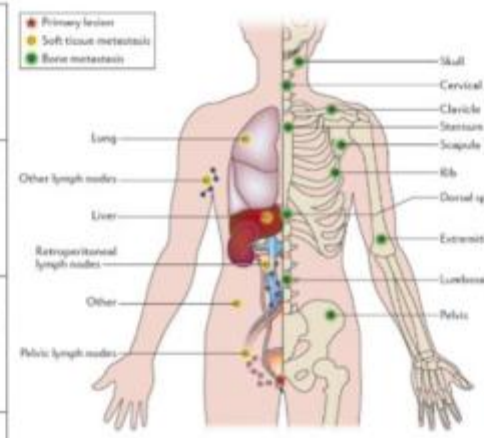
- The core WB-MRI protocol when used alone is designed for bone and lymph node metastasis detection (should be completed within 30 min of table time). More comprehensive assessments (core plus extensions) should be used for patients with established metastatic including visceral disease. Depending on the sequences used, comprehensive assessments can be completed within 45–50 min of table time.

- Since the mid-2010s, research has focused on the standardization and therapy monitoring of WB-MRI.
- Padhani et al. highlighted the need for expert recommendations for WB-MRI scans and developed the Metastasis Reporting and Data System for Prostate Cancer (METRADS-P). An expert panel of the most experienced radiologists and nuclear medicine physicians in advanced prostate cancer imaging conducted a review and formulated guidelines on the performance standards for WB-MRI for the assessment of multi-organ involvement in advanced prostate cancer.
- Padhani et al. also reported the usefulness of WBMRI for therapy monitoring. In addition, Padhani et al. suggested that WB-MRI provides a clear categorization of bone metastasis response and that the accurate assessment of therapy response would aid the rationale development of targeted therapies.

Name ID DOB

Physician Exam date current Exam date comparator

Soft tissues RECIST criteria	MET-RADS Prostate Report	Bones MET-RADS criteria



Primary
Involved Y N
RAC 1+ 2+
Comment

Pelvic nodes
Involved Y N
RAC 1+ 2+
Comment

Retroperitoneal
Involved Y N
RAC 1+ 2+
Comment

Other nodes
Involved Y N
RAC 1+ 2+
Comment

Liver
Involved Y N
RAC 1+ 2+
Comment

Lungs
Involved Y N
RAC 1+ 2+
Comment

Other sites
Involved Y N
RAC 1+ 2+
Comment

OVERALL ASSESSMENT

	No dis	CR	PR	SD	PD	Mixed
Primary						Minor or major
Nodes						No progressive lesions overall SD/PR assessments
Viscera						
Bones			RAC 1/2?	RAC 3	RAC 4/5	

Comments

Skull
Involved Y N
RAC 1+ 2+
Comment

Cervical spine
Involved Y N
RAC 1+ 2+
Comment

Dorsal spine
Involved Y N
RAC 1+ 2+
Comment

Lumbosacral spine
Involved Y N
RAC 1+ 2+
Comment

Pelvis
Involved Y N
RAC 1+ 2+
Comment

Thorax
Involved Y N
RAC 1+ 2+
Comment

Limbs
Involved Y N
RAC 1+ 2+
Comment

Response assessment categories (RAC): 1 Response: highly likely; 2 Response: likely; 3 Stable; 4 Progression: likely; 5 progression: highly likely. Single lesion 1° RAC only; ≥2 lesions or diffuse disease use both RACs

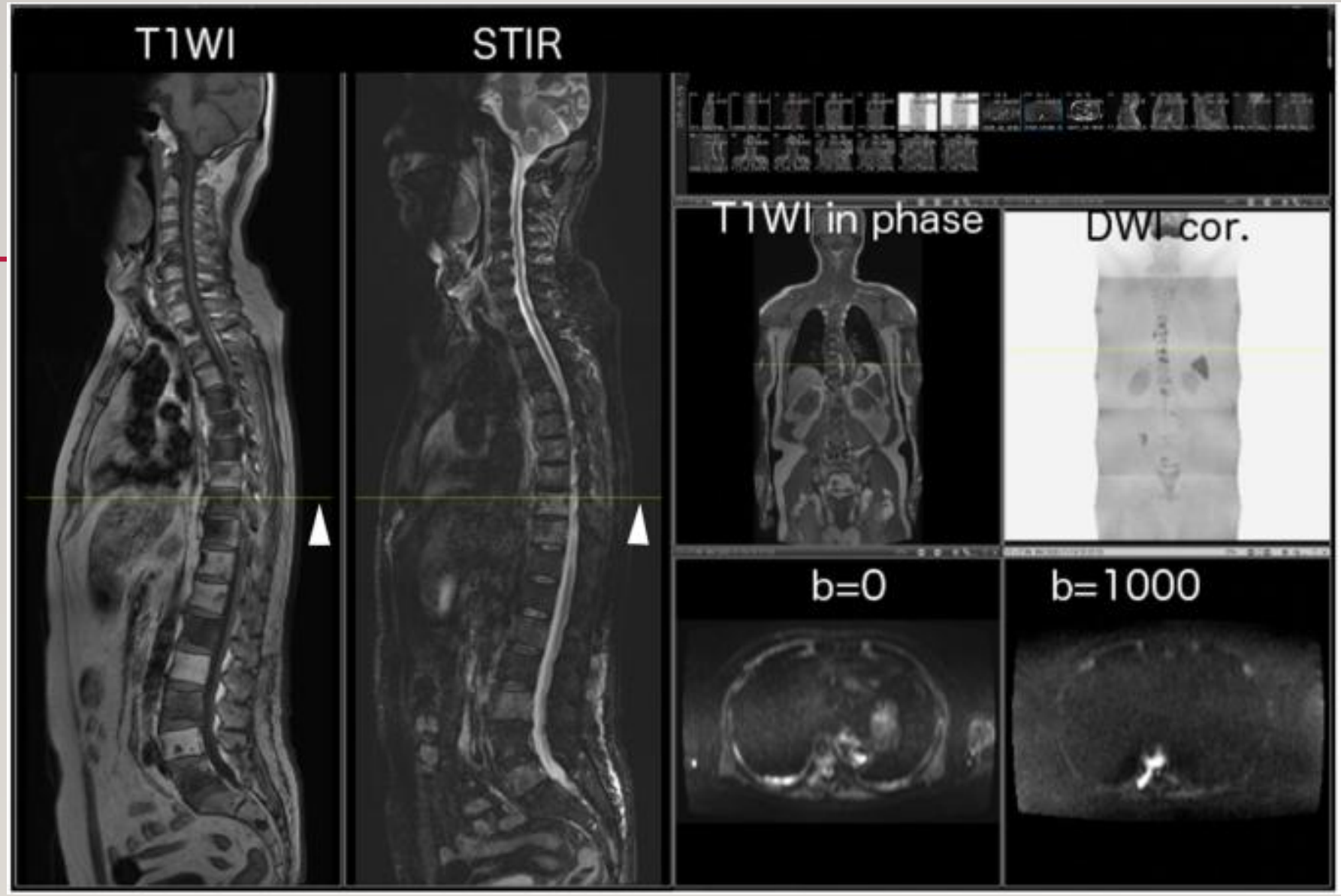
Metastasis Reporting and Data System for Prostate Cancer: Practical Guidelines for Acquisition, Interpretation, and Reporting (MET-RADS-P) of Whole-body MRI Evaluations of Malignant Involvement in Advanced Prostate Cancer. Eur Urol. 2017; 71:81-92

Radiologist Date

Fig. 4 MET-RADS-P template [65]. The MET-RADS-P template form allocates the presence of unequivocally identified disease to 14 predefined regions of the body

Table 3 – METastasis Reporting and Data System for Prostate Cancer regional response assessment categories

RAC	Classification	Region	Descriptions[a]
1	Highly likely to be responding	Local, nodal, and visceral Bone	• Consistent with RECIST v1.1/PCWG criteria for unequivocal response (partial/complete; see below) Return of normal marrow in areas previously infiltrated by focal/diffuse metastatic infiltration • Decrease in number/size of focal lesions sufficient to indicate high likelihood response • Evolution of diffuse neoplastic pattern to focal lesions Decreasing soft tissue associated with bone disease • Dense lesion sclerosis (edge to edge), sharply defined, very thin/disappearance of hyperintense rim on T2W-FS images • The emergence of intra/peritumoural fat within/around lesions (fat dot/halo signs) • Previously evident lesion shows increase in ADC from ≤1400 $\mu m^2/s$ to >1400 $\mu m^2/s$[b] • ≥40% increase in ADC from baseline with corresponding decrease in high b-value SI; and morphological findings consistent with stable or responding disease[c]
2	Likely to be responding	Local, nodal, and visceral Bone	• Changes depicting tumour response that do not meet RECIST v1.1/PCWG criteria for partial or complete response (see below) Evidence of improvement, but not enough to fulfil criteria for RAC 1. For example: • Previously evident lesions showing increases in ADC from ≤1000 $\mu m^2/s$ to <1400 $\mu m^2/s$[b] • >25% but <40% increase in ADC from baseline with corresponding decrease in high b-value SI; and morphological findings consistent with stable or responding disease[c]
3	No change	All	• No observable change
4	Likely to be progressing	Local, nodal, and visceral Bone	• Changes depicting tumour progression that do not meet RECIST v1.1/PCWG criteria for progression (see below) • Evidence of worsening disease, but not enough to fulfil criteria for RAC 5 • Equivocal appearance of new lesion(s) • No change in size but increasing SI on high b-value images (with ADC values < 1400 $\mu m^2/s$) consistent with possible disease progression[b] • Relapse disease: re-emergence of lesion(s) that previously disappeared or enlargement of lesion(s) lesions that had partially regressed/stabilized with prior treatments Imaging depicted bone lesions that might be clinically significant (therefore excludes asymptomatic fractures in noncritical bones) • Soft tissue in spinal canal causing narrowing not associated with neurological findings and not requiring radiotherapy
5	Highly likely to be progressing	Local, nodal, and visceral Bone	• Changes depicting tumour progression that meet RECIST v1.1/PCWG criteria for unequivocal progression (see below) • New critical fracture(s)/cord compression requiring radiotherapy/surgical intervention → only if confirmed as malignant by MRI signal characteristics • Unequivocal new focal/diffuse area(s) of metastatic infiltration in regions of prior normal marrow • Unequivocal increase in number/size of focal lesions Evolution of focal lesions to diffuse neoplastic pattern • Appearance/increasing soft tissue associated with bone disease

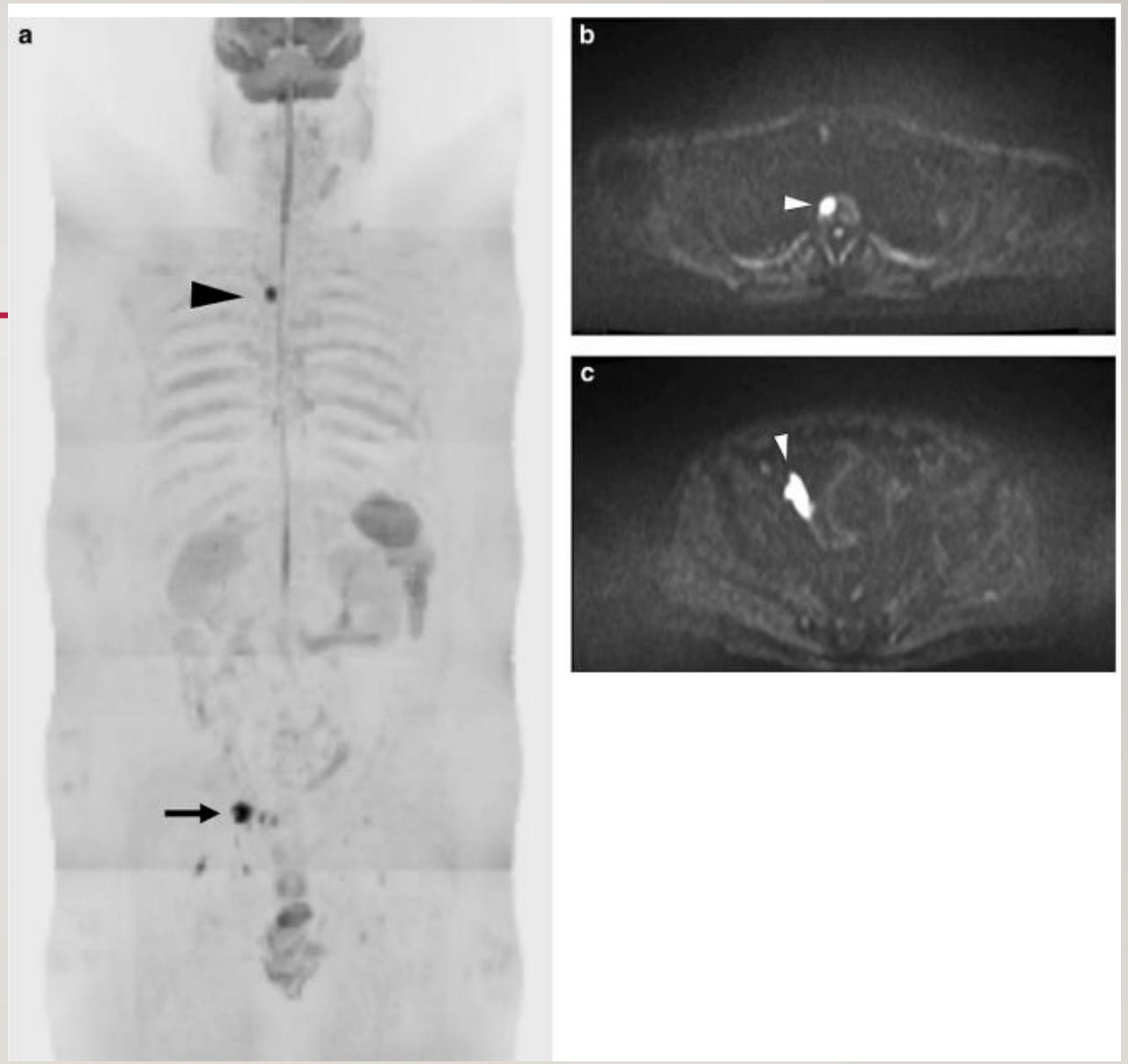

T1WI
STIR
T1WI in phase
DWI cor.
b=0
b=1000

INTERPRETATION OF IMAGING METHODS WITH WB-MRI
RECOMMENDED IMAGING METHODS AND PARAMETERS

The total examination time, including the positioning of the patient, is approximately 23 min.
After image acquisition, image processing is performed.

From the axial DWI images, coronal and radial images are reconstructed and displayed as black-and-white reversed images.

In-phase coronal T1WI- and DWI-coronal reconstructed images are fused, and the fusion images are reconstructed.



Oligometastases. An 82-year-old man with bone metastases from prostate cancer.

a On the radial reconstructed antero-posterior DW image, a high-intensity area was observed in Th2, and swelling of the right internal iliac lymph node was suspected. At this time, the serum PSA was 34.903 ng/mL.

b On the *b*= 1000 axial DW image at the level of the Th2, a high-intensity area was seen.

c On the *b*= 1000 axial DW image at the level of the pelvis, the right iliac lymph node was swollen and had shown high intensity.

SOME TYPICAL CASES OF BONE METASTASES IN PROSTATE CANCER

1.Primary osteoblastic metastases: frequently observed in prostate cancer in the initial stage. osteosclerotic change is evident on CT images and appears as low intensity on T1WI images and high intensity on DWI images.

2. Primary mixed-type metastases/inter-trabecular metastases: CT images do not show the abnormal findings, such as bone formation or destruction, and DWI of MRI show high signal intensity.

3. Primary unknown osteoblastic metastases histologically confirmed as prostate cancer: In such cases, multiple high-intensity areas are noted in WB-DWI images, and these are diagnosed as multiple bone metastases. In addition, the prostate gland is carefully observed on axial and coronal reconstructed DWI images. Predicting the primary site before assessing for high serum PSA levels is sometimes possible.

4. Therapeutic effect of bone metastases. For monitoring the therapeutic effect, both therapy reactive lesions and newly recurred lesions are often observed in the same case. DWI enables precise evaluation of such lesions.
Radiologists should be aware that a CT finding of osteosclerotic change in metastatic lesions has two possibilities: One is the osteoblastic metastasis itself and the other is the re-ossification of the therapeutic effect.

5. Oligometastases. is an intermediate state of distant spread, reflecting disease with a low, slow and late metastatic spreading capacity.
the presence of three synchronous metastases (bone and/or lymph nodes) should be used to define oligo-metastatic prostate cancer. However, conventional imaging modalities, which include CT findings, have low sensitivity in detecting small-volume disease and may underestimate disease burden. Therefore, WBMRI has been offered as a modality for effectively detecting oligo-metastases

FUTURE EVOLUTION OF WB-MRI USE OF ARTIFICIAL INTELLIGENCE (AI)

- AI has been mainly adopted to reduce scanning time
- deep learning-based noise reduction for brain MRI. In addition,
- deep learning-based reconstruction for denoising brain, lumbar spine, and knee images, with the ultimate goal of shorting scanning time and reduce noise.
- AI with WB-DWI. Their study aimed to improve the image quality of repeated acquisition (NEX) to one image and considerably reduce scanning times and found that image quality was improved and the acquisition time was reduced from 30 to 5 min.
- automatic segmentation of lesions and the removal of normal structures are required for AI when the tDV and mean ADC are calculated

NOVEL MOLECULAR PET/CT OR PET/MRI TRACERS

PET/CT or PET/MRI with tracer	Development of specific radioactive tracers for cellular structure and function	Radiation exposure Expensive
^{11}C-choline	Reimbursed by Medicare In restaging, detection rate <20% if PSA level <1 ng/mL, 46% if PSA level 1–3 ng/mL, and 82% if PSA level >3 ng/mL (9)†	Short half-life (20 minutes) necessitates on-site cyclotron
^{18}F-fluciclovine	Reimbursed by Medicare Promising clinical evidence in setting of restaging In restaging, detection rate is 21% if PSA level <1 ng/mL, 45% if PSA level 1–3 ng/mL, and 59% if PSA level >3 ng/mL (10)†	Moderate specificity and moderate performance at low PSA level cutoffs
Gallium 68 (^{68}Ga) PSMA	In restaging, detection rate is 58% if PSA level 0.2–0.5 ng/mL, 73% if PSA level 0.5–1.0 ng/mL, and >90% if PSA level >1 ng/mL (11)† Can guide to targeted therapy with lutetium 177 (^{177}Lu) PSMA	Investigative and not yet approved by FDA

- New PET tracers in prostate cancer are promising and have shown improved accuracy in detection and restaging of recurrent prostate cancer compared with conventional imaging.
  Sodium Fluoride.—18F–sodium fluoride is an analog of the hydroxyl group in hydroxyapatite bone crystals and a nonspecific molecular imaging biomarker of osteoblastic activity

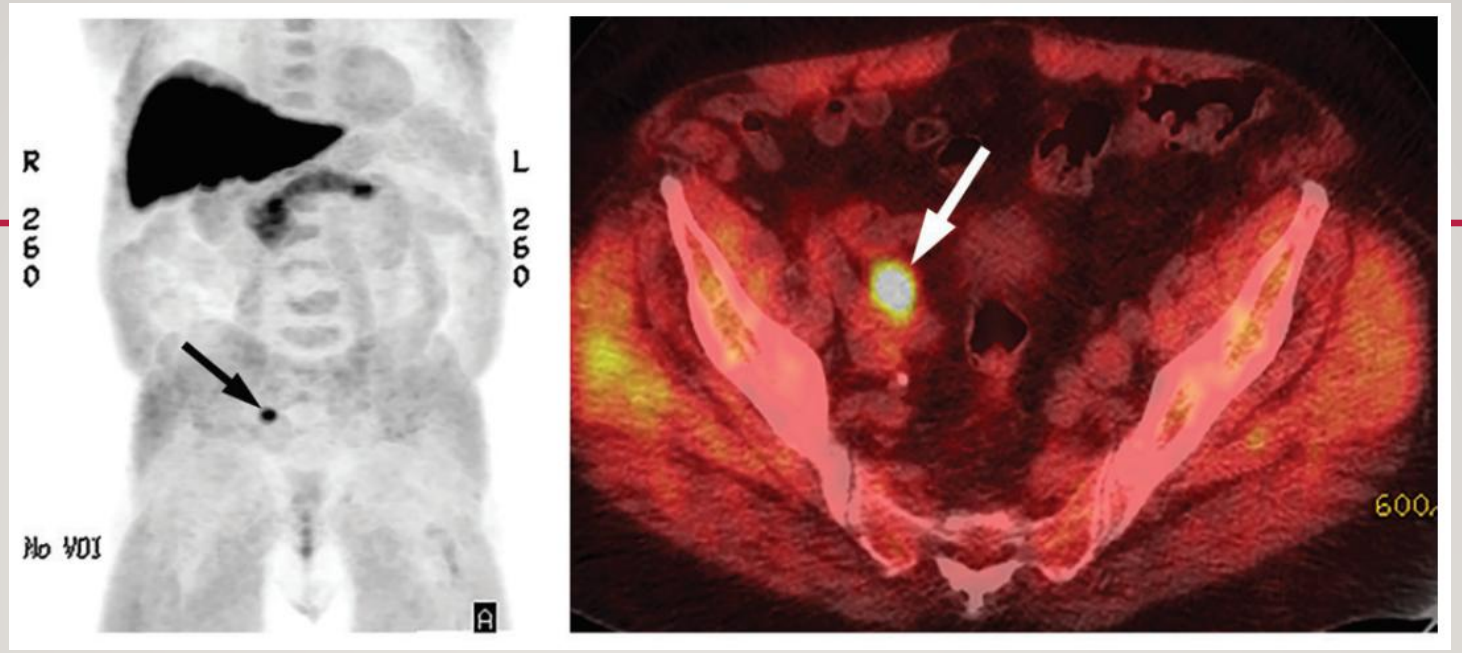
- ***Choline.—***Choline is a precursor of phospholipid, which is an important major component of all cell membranes. The clinical value of choline PET in prostate cancer is in evaluation of local recurrence, lymph node metastases, and bone metastases after primary definitive therapy, at a PSA level greater than 1–2 ng/mL. Choline PET is superior to CT and MRI for imaging of lymph node metastasis. However, inflammatory lesions and other benign and malignant tumors (eg, parathyroid adenoma, invasive thymoma) can cause false-positive lesions.

Fluciclovine.—The FDA approved 18Ffluciclovine for detection of biochemical recurrence of prostate cancer in 2016. In prostate cancer, the principal utility is evaluation of local recurrence, lymph node metastases, and bone metastases after primary definitive therapy. Some reports suggest that fluciclovine PET is superior to choline PET for detecting recurrence. Inflammatory lesions, benign tumors, and other malignant tumors(eg, lung, brain) can cause false-positive lesions.

- ***Prostate-specific Membrane Antigen.—***Prostates pecific membrane antigen (PSMA) is a type II transmembrane glycoprotein with an extensive extracellular domain providing an excellent target for imaging, a transmembrane segment, and an intracellular domain and acts as a glutamate carboxypeptidase enzyme.
- PSMA expression is 100–1000-fold higher in prostate cancer than in other tissues. Gallium 68 (68Ga) PSMA is a small molecule that binds to the extracellular domain of PSMA and was developed as a new investigative PET tracer for recurrent prostate cancer. 68Ga-PSMA PET has been shown to improve diagnostic performance and allows selection of patients who may benefit from lutetium 177 (177Lu)–labeled PSMA peptide receptor radionuclide therapy (PRRT) in metastatic CRPC (phase III clinical trial) .
- 68Ga-PSMA PET has been demonstrated to be superior to 11C-choline and 18F-fluciclovine PET in depicting recurrent prostate cancer, especially when PSA level is less than 1.0 ng/mL. Normal ganglia (eg, celiac ganglia) and the neovasculature of tumors or benign conditions can cause false-positive lesions . In addition, non-PSMA–producing prostate cancers such as those that are poorly differentiated or have neuroendocrine features may not be revealed well with 68Ga-PSMA PET/CT.

Table 2: Advantages and Disadvantages of Current Imaging Techniques for Prostate Cancer Recurrence

Imaging Modality by Type	Indications and Advantages	Disadvantages
Posttreatment imaging of prostate or prostatic fossa*		
Transrectal US	Used mostly for guiding prostate biopsy for tissue characterization	Limited tissue contrast between cancerous and benign tissue Cancer restaging is difficult
Multiparametric MRI	Indicated in biochemical recurrence after radiation treatment Used to guide targeted biopsy in irradiated prostate using MRI/US fusion software and in suspected locally recurrent tumor after prostatectomy	Morphologic and functional changes after primary therapy may decrease diagnostic performance Susceptible to artifacts Expensive Not portable
Bone imaging		
Bone scanning (technetium 99m [99mTc]–labeled methylene diphosphonate [MDP])	Widely available Whole-body imaging Useful for detecting osteoblastic metastasis Commonly used for posttreatment follow-up	Osteolytic metastasis can lead to false-negative diagnosis Bone scan flare response Poor spatial resolution Radiation exposure When results are inconclusive, additional imaging (skeletal radiography, CT, MRI, or ^{18}F–sodium fluoride PET/CT) is required
^{18}F–sodium fluoride PET/CT	Superior sensitivity to that of conventional bone scanning Faster acquisition time than conventional bone scanning	Not reimbursed by Medicare Not tumor specific Flare response phenomenon
Soft-tissue imaging		
CT	Widely available Useful for detecting bone involvement and nodal staging	Poor soft-tissue contrast of prostate and periprostatic soft-tissue structure as well as prostatic fossa after radical prostatectomy Radiation exposure
MRI of abdomen or pelvis	Excellent tissue contrast Allows functional imaging No radiation exposure	Morphologic and functional changes after primary therapy may decrease diagnostic performance Expensive Susceptible to artifacts
PET/CT or PET/MRI with tracer	Development of specific radioactive tracers for cellular structure and function	Radiation exposure Expensive
^{11}C-choline	Reimbursed by Medicare In restaging, detection rate <20% if PSA level <1 ng/mL, 46% if PSA level 1–3 ng/mL, and 82% if PSA level >3 ng/mL (9)†	Short half-life (20 minutes) necessitates on-site cyclotron
^{18}F-fluciclovine	Reimbursed by Medicare Promising clinical evidence in setting of restaging In restaging, detection rate is 21% if PSA level <1 ng/mL, 45% if PSA level 1–3 ng/mL, and 59% if PSA level >3 ng/mL (10)†	Moderate specificity and moderate performance at low PSA level cutoffs
Gallium 68 (^{68}Ga) PSMA	In restaging, detection rate is 58% if PSA level 0.2–0.5 ng/mL, 73% if PSA level 0.5–1.0 ng/mL, and >90% if PSA level >1 ng/mL (11)† Can guide to targeted therapy with lutetium 177 (^{177}Lu) PSMA	Investigative and not yet approved by FDA



Lymph node metastasis in an 83-year-old man with a history of high-intensity focused ultrasound ablation therapy with ADT for prostate cancer 9 years earlier, followed by salvage radiation therapy 2 years later. His PSA level increased to 16.7 ng/mL from 3.1 ng/mL 18 months earlier. Frontal maximum intensity projection (MIP) $_{18}$F-fluciclovine PET image (a) and axial $_{18}$F-fluciclovine PET/CT image (b) show
a single intensely avid right external iliac lymph node (arrow). The patient completed external-beam radiation therapy and is being followed up.

68 GA-PSMA-PET OR WB-MRI?

- 68 Ga-PSMA-PET has shown to be more accurate than WB-MRI in identifying distant metastases. It is particularly effective in cases where PSA is lower than 0.5 ng/ml.
- However, the advantage of WB-MRI is its absence of radiation exposure, cost-effectiveness, and examination repeatability. Thus, the combination of WBMRI and these tracers might be the next trend in research
- WB-MRI has been established as the gold standard for detecting bone metastases from prostate cancer. It has the advantages of being able to detect lesions that are overlooked by conventional modalities, such as CT and BS. Moreover, because of its repeatability, it can be used to monitor therapeutic effects. In addition, further shortening of imaging time and automatic image processing will likely continue to progress.

NCCN GUIDELINES FOR IMAGING USE IN RECURRENT PROSTATE CANCER

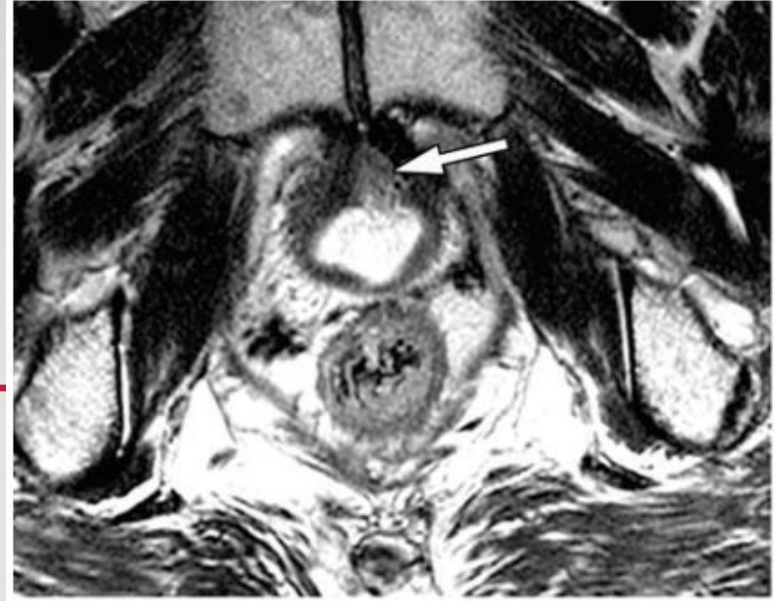
- The National Comprehensive Cancer Network (NCCN) published guidelines in 2019 for use of imaging studies in workup of asymptomatic patients with biochemical recurrence after radical prostatectomy or radiation therapy.
- The NCCN guidelines state that workup for progression to metastatic disease after failed salvage therapy should include:

  bone imaging, chest CT, and abdominopelvic CT or MRI with or without contrast material. 11C-choline or 18F-fluciclovine PET/CT or PET/MRI for further soft-tissue evaluation or 18F–sodium fluoride PET/CT for further bone evaluation can be considered.

Table 3: Use of Imaging Studies in Patients with Biochemical Recurrence after Radical Prostatectomy or Radiation Therapy

Type of Biochemical Recurrence	Indication	Candidacy for Local Therapy*	Tests for Risk Stratification	Imaging Studies Considered
After radical prostatectomy	PSA level persistence or recurrence	Not applicable	PSADT	Bone imaging Chest CT Abdominopelvic CT or MRI ^{11}C-choline or ^{18}F-fluciclovine PET/CT or PET/MRI Prostate bed biopsy (especially if imaging results suggest local recurrence)
After radiation therapy	PSA level persistence or recurrence or positive DRE results	Candidates	PSADT Bone imaging Prostate MRI Transrectal US–guided biopsy	Chest CT Abdominopelvic CT or MRI ^{11}C-choline or ^{18}F-fluciclovine PET/CT or PET/MRI
		Noncandidates	…	Bone imaging

Source.—Reference 2.
Note.—DRE = digital rectal examination, PSADT = PSA level doubling time.
*Criteria for candidacy for local therapy are original clinical stage T1 or T2 and NX or N0, life expectancy >10 years, and PSA level now <10 ng/mL.



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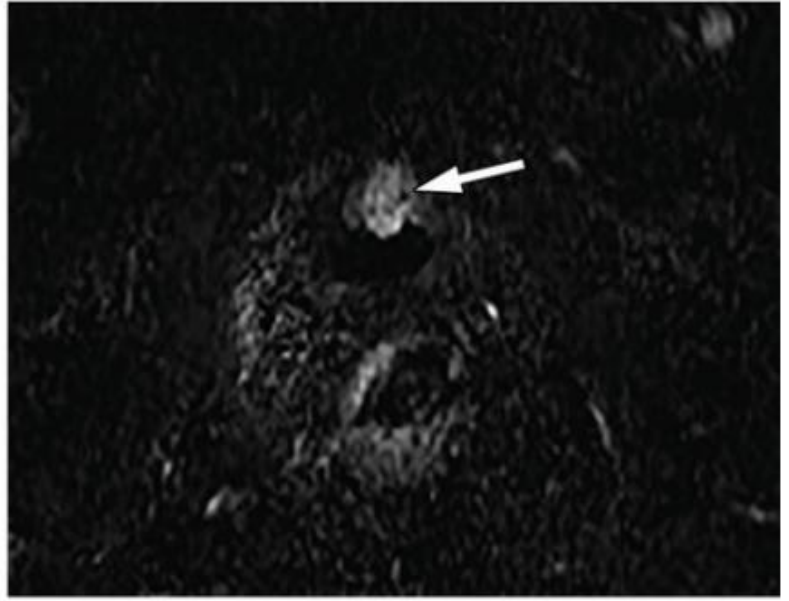

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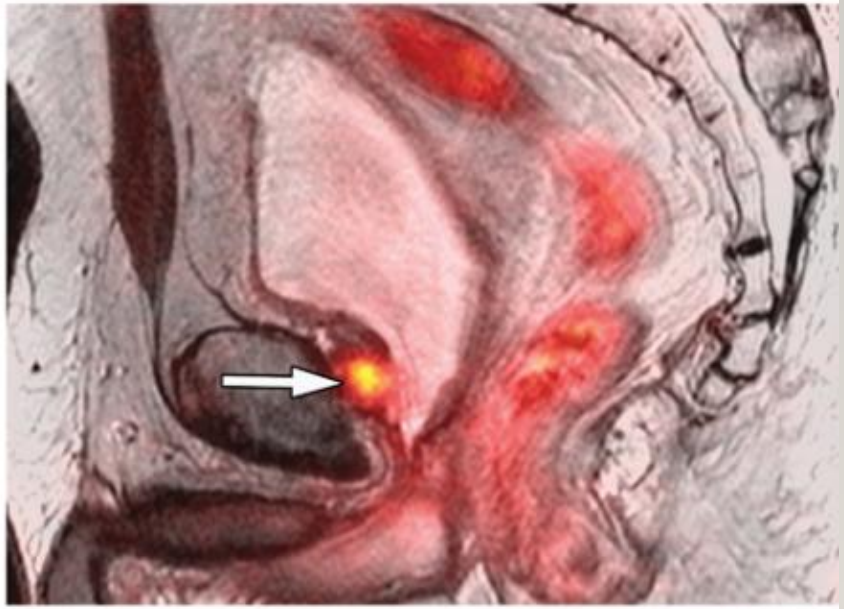


Locally recurrent tumor in a 67-year-old man with rising PSA level of 1.4 ng/mL 8 years after radical prostatectomy for prostate cancer (Gleason score 3 + 4 = 7, stage pT2c) and 5 years after salvage radiation therapy and ADT.

(a) Axial T2-weighted image from ^{11}C-choline PET/multiparametric MRI shows a nodule in the anterior bladder neck region

(b) (b) Dynamic contrast-enhanced image with fat saturation 32 seconds after starting intravenous injection of contrast material shows hyperenhancement of the lesion.

(c) (c) Sagittal image from ^{11}C-choline PET/T2-weighted MRI shows that the lesion has focal increased activity, with maximum standardized uptake value (SUV) of 4.6.

(d) After ADT, the PSA level became undetectable (<0.1 ng/mL).

IMAGING FINDINGS OF PROSTATE CANCER RECURRENCE- LOCAL RECURRENCE

- The characteristic multiparametric MRI findings of locally recurrent tumor after radical prostatectomy: a hyperenhancing soft-tissue nodule in the prostatectomy fossa, which is isointense to muscle on T1-weighted images and slightly hyperintense on T2-weighted images with restricted diffusion.
- Typical locations include the perianastomotic vesicourethral region (50%– 60%), retrovesical region or seminal vesicles (10%–30%), bladder neck or base (10%–20%), ureter at the vesicoureteral junction, and stump of the vas deferens.
- Previous reports showed sensitivity for local recurrence of 48%–100% and specificity of 52%–100%; detection rates for local recurrence in patients not receiving ADT were 77% for PSA level less than 0.4 ng/mL, 70% for PSA level of 0.4–1.0 ng/mL, and 76%–83% for PSA level greater than 1.0 ng/mL
- Ureteral obstruction may be caused by direct tumor extension to the ureter at the vesicoureteral junction.

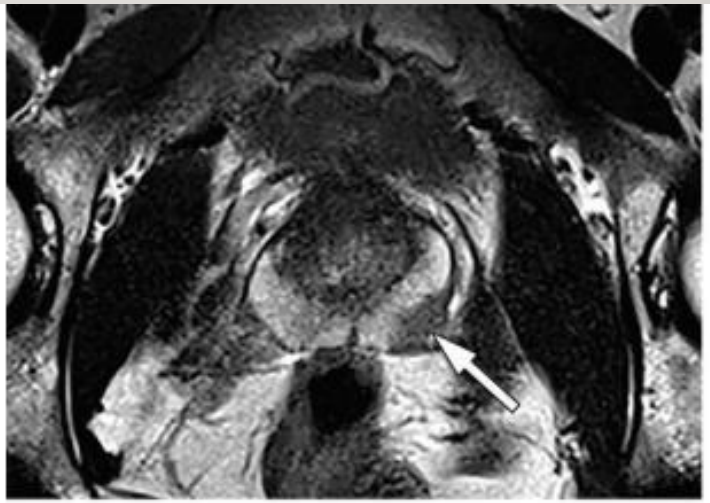
- Multiparametric MRI may still be useful in monitoring for recurrence , although administration of ADT before multiparametric MRI may reduce sensitivity and accuracy for detection of treated or recurrent viable prostate cancer.
- Transrectal US–guided biopsy of the prostatectomy bed is considered if local recurrent tumor is suspected at multiparametric MRI or other imaging studies because the yield of biopsy has been shown to be lower with negative multiparametric MRI results. MRI/US fusion software is not currently available in the postprostatectomy setting.

After radiation therapy, recurrent tumor appears at multiparametric MRI as: a hyperenhancing nodular lesion in the treated prostate, often associated with restricted diffusion, frequently in the same location as the pre–radiation therapy tumor. Other features include growth of the lesion with progressive bulging of the prostatic capsule over time

The lesion frequently appears inconspicuous on T2-weighted images because a previously irradiated prostate typically appears diffusely hypointense with obliteration of zone differentiation on T2-weighted images.

Simultaneous PET/ MRI and multiparametric MRI of the prostate may play an important role in evaluating patients after initial therapy including focal therapy.
Whenever feasible, MRI-targeted biopsy under transrectal US guidance should be considered after radiation therapy and focal ablation for the tissue diagnosis because of a significant rate of false-positive imaging results.

Locally recurrent tumor in a 57-year-old man with biochemical recurrence and PSA level of 1.5 ng/mL 2.5 years after focal laser ablative therapy for prostate cancer (Gleason score 3 + 4 = 7).
(a) Pretreatment axial T2-weighted image shows a lesion in the left posterolateral peripheral zone at the midgland. (b) Axial T2-weighted image from ^{11}C-choline PET/MRI shows posttreatment changes with scarring and distortion of the left lobe and a 1.0-cm lesion on the left. (c) Corresponding axial image from ^{11}C-choline PET/MRI shows that the lesion has choline avidity, with maximum SUV of 2.5. Subsequent MRI/US–guided targeted biopsy demonstrated adenocarcinoma (Gleason score 3 + 4 = 7). Salvage radical prostatectomy was performed.



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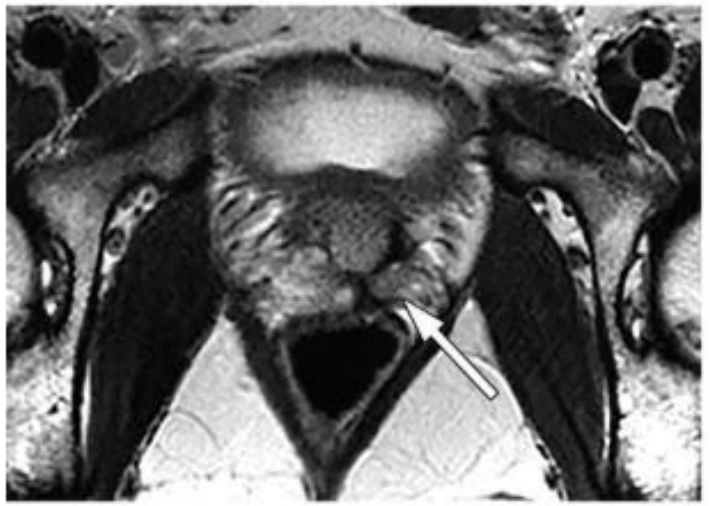
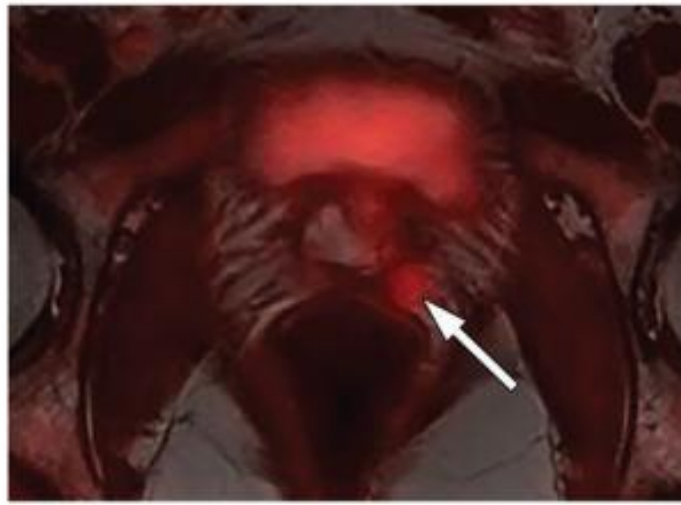




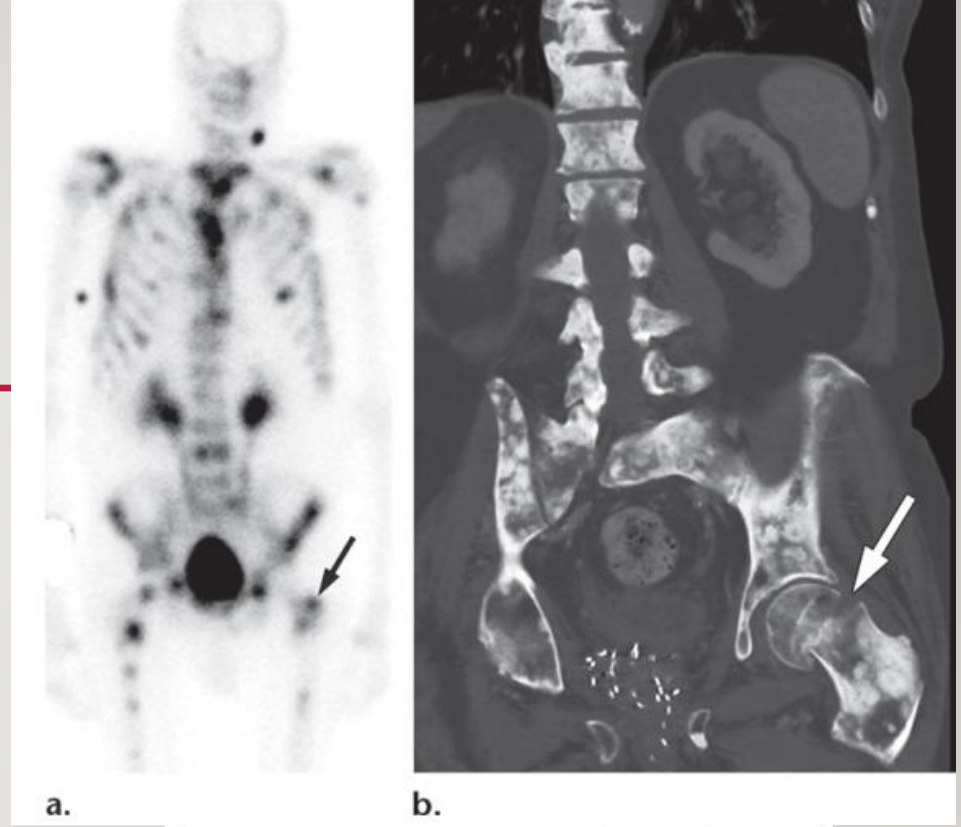
PATTERNS OF SYSTEMIC METASTASIS

- The most common metastatic sites besides bone were the lymph nodes, liver, thorax (lung and pleura), and adrenal gland.
- Uncommon metastatic sites included the peritoneum, brain or leptomeninges, kidney, and ureter or urethra;
- other rare sites included the stomach or bowel, spleen, pancreas, breast, gallbladder, penis, and scrotum.
- The presence of visceral metastatic disease is an adverse prognostic factor for overall survival in men with metastatic CRPC.
- Men with liver metastasis have the worst overall survival, followed by those with metastases to the lung, bones, and lymph nodes.

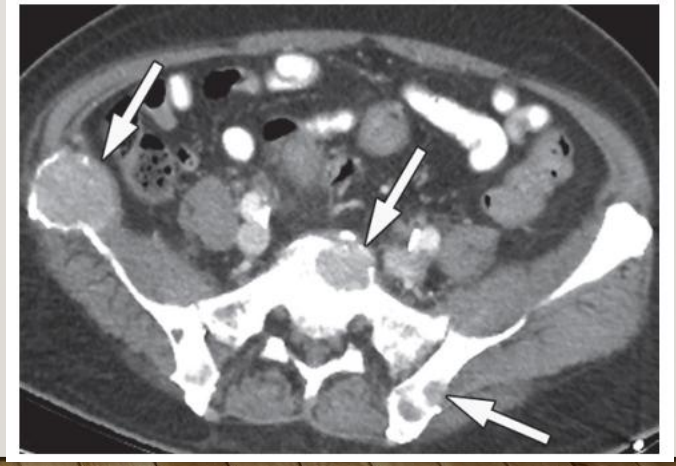
BONE METASTASIS

- Occurs in approximately 90% of patients with metastatic prostate cancer in autopsy series.
- Bone metastases usually appear osteoblastic with slower progression than those from other tumors , while osteolytic metastases tend to be more aggressive

Osteoblastic bone metastases with a pathologic fracture in an 84-year-old man with metastatic CRPC, metastatic bone involvement, and PSA level of 41.8 ng/mL. He recently experienced a fall.
(a) ^{99m}Tc-MDP bone scan shows multiple diffuse foci of increased tracer uptake, characteristic of skeletal metastases. (b) Coronal CT image (bone window) shows multiple diffuse sclerotic metastases and a pathologic fracture (arrow) of the left femoral neck, which demonstrates ^{99m}Tc-MDP tracer uptake on the bone scan (arrow in a). Left hemiarthroplasty was performed.

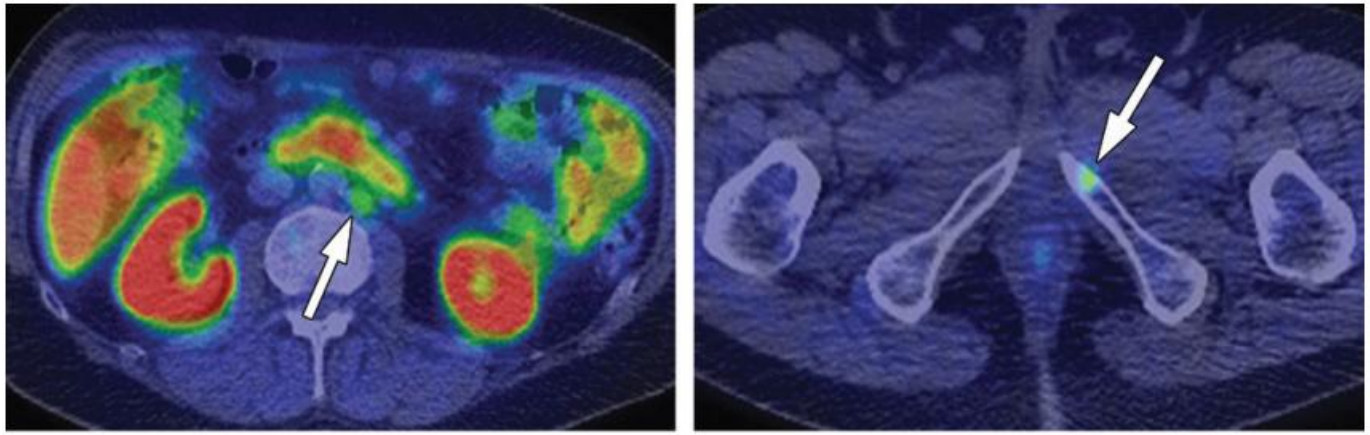


Lytic bone metastases in a 72-year-old man with CRPC, metastatic bone and lymph node involvement, and PSA level of 61 ng/mL. Axial CT image shows multifocal osteolytic metastases (arrows)



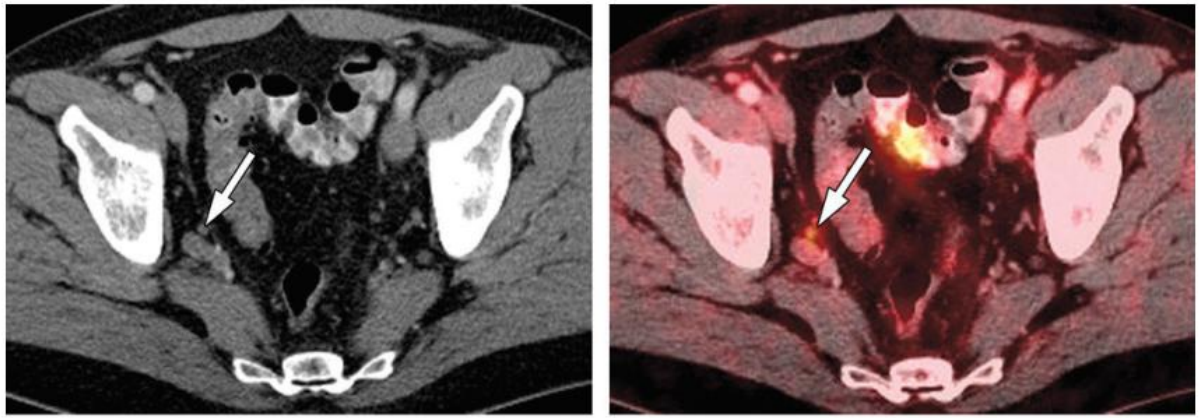
LYMPH NODE METASTASIS

- Any previous treatment in the pelvis such as surgical lymphadenectomy or radiation therapy can modify the nodal dissemination pathways, and then recurrent disease might initially be seen in extrapelvic nodes. Although rare, supradiaphragmatic (eg, mediastinal, hilar, or supraclavicular) lymph node involvement can be the first clinical or imaging manifestation of metastatic prostate cancer.
- At conventional CT and MRI, the diagnosis is largely based on size criteria, with resulting limitations in sensitivity or specificity depending on the chosen cutoff,
- MR lymphography with iron oxide particles is currently under development and appears to improve lymph node staging of prostate cancer.
- Molecular PET/CT or PET/MRI with choline, fluciclovine, or PSMA has improved the sensitivity for small-volume lymph node metastases.



a. b.

Figure 7. Small-volume oligometastases to a lymph node and bone in a 67-year-old man with biochemical recurrence and PSA level of 1.4 ng/mL 2 years after radical prostatectomy for prostate cancer (Gleason score 4 + 4 = 8, pT3bN0). Axial ^{11}C-choline PET/CT images show choline-avid nodal metastases in the left para-aortic retroperitoneum (arrow in **a**) and left inferior pubic ramus (arrow in **b**). Subsequent choline PET/CT after ADT and radiation therapy to the prostatic fossa, pelvis, and para-aortic lymph nodes revealed near-resolution in size and choline avidity of the left para-aortic lymph node and left pubic bone lesion (not shown). The PSA level became undetectable (<0.1 ng/mL).



a. b.

Figure 8. Small-volume metastasis to a lymph node in a 55-year-old man with biochemical recurrence and PSA level of 0.5 ng/mL 7 years after radical prostatectomy for prostate cancer. Axial nonenhanced CT image **(a)** and ^{68}Ga-PSMA PET/CT image **(b)** show a normal-sized right internal iliac lymph node (arrow) with mild PSMA avidity (maximum SUV = 1.9). Pelvic lymphadenectomy demonstrated that the lesion was metastatic prostate adenocarcinoma.

LUNG AND PLEURAL METASTASIS

- CT findings include solitary or multiple lung nodules or masses (39% and 55%, respectively), pleural nodules or masses (12%), and lymphangitic carcinomatosis (12%). Supradiaphragmatic lymphadenopathy may be concomitantly present in 76% of patients, and osseous metastasis may be concomitantly present in 61%.

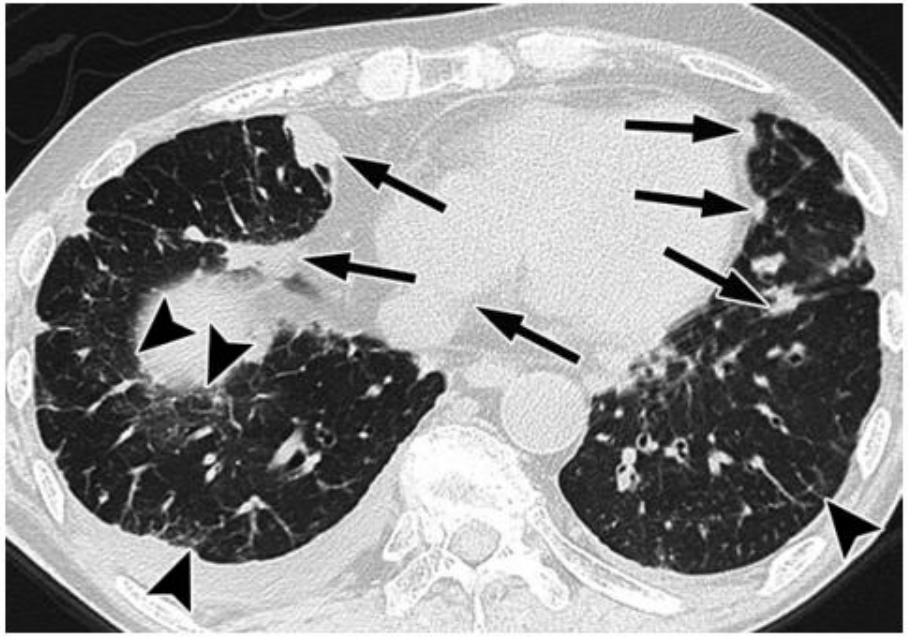
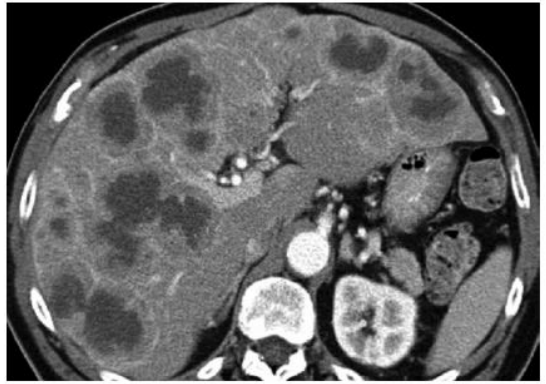
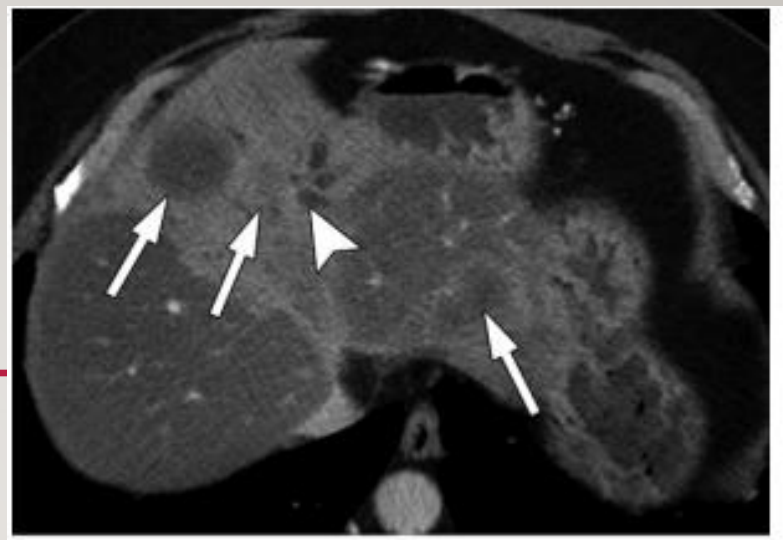


Figure 9. Pleuropulmonary metastases in a 77-year-old man with CRPC, local recurrent disease, metastatic lymph node and bone involvement, and PSA level of 167 ng/mL. CT image (lung window) shows intralobular septal thickening (arrowheads) of lymphangitic carcinomatosis and pleural nodules (arrows).

LIVER METASTASIS





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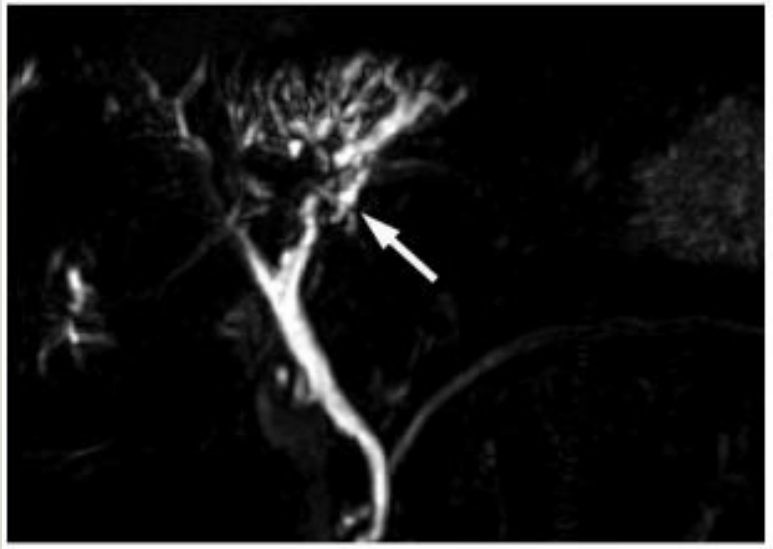
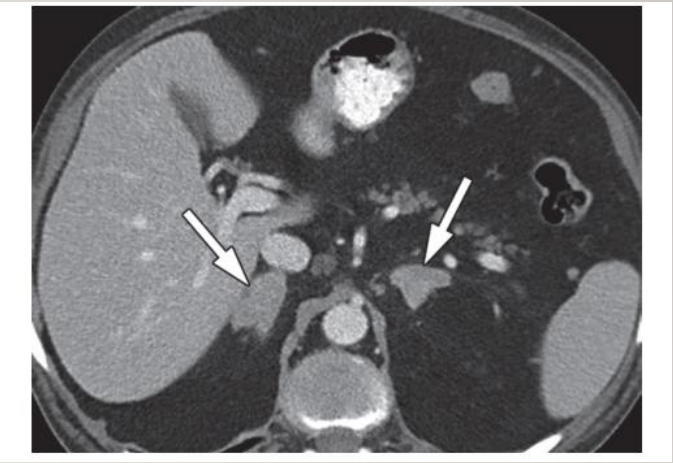


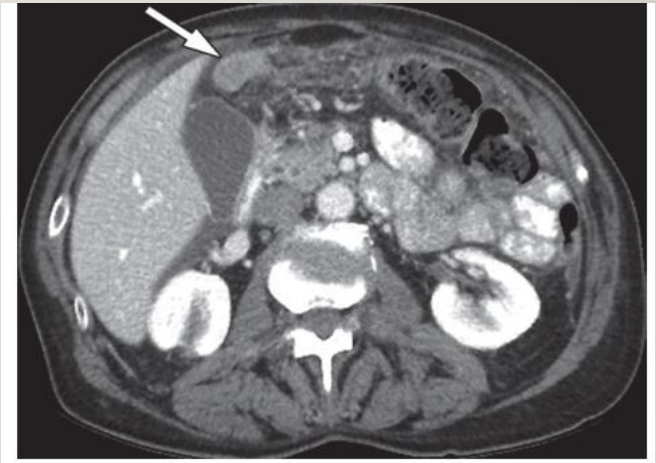
- Liver metastasis from prostate cancer occurs late in the course of the disease and is frequently associated with neuroendocrine tumor characteristics.
- The presence of liver metastasis is associated with the worst overall survival.
- Imaging findings include solitary or more frequently multiple hypoenhancing hepatic masses and—to a lesser degree—infiltrative hepatic masses with or without associated peripheral bile duct dilatation.
- 68Ga-PSMA PET is superior to 11C-choline and 18F-fluciclovine PET for detection of liver metastasis from prostate cancer because physiologic background uptake in the liver parenchyma obscures hepatic lesions at 11C-choline and 18Ffluciclovine PET.

ADRENAL AND PERITONEAL METASTASIS

- Adrenal involvement is often associated with multiple organ metastases. Adrenal insufficiency secondary to bilateral adrenal involvement by prostate cancer occasionally develops. Imaging findings include solitary or multiple adrenal masses.

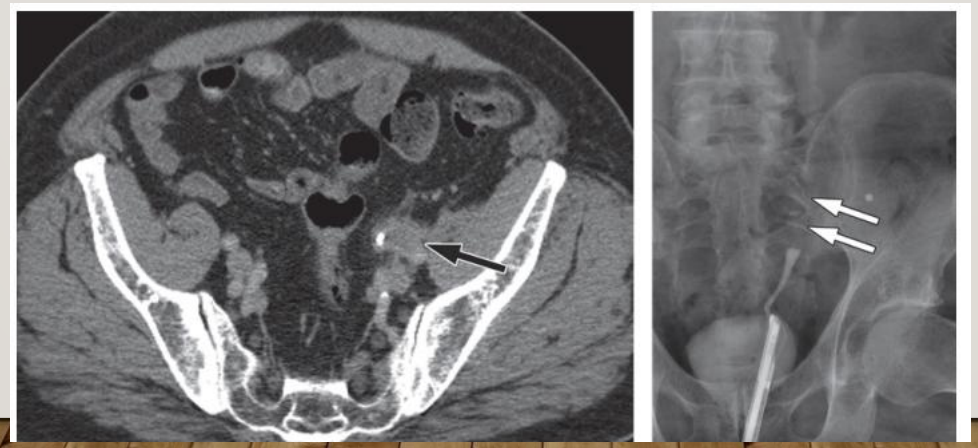


- Metastatic involvement of the peritoneum is rare. Causes of peritoneal metastasis can be tumor behavior (eg, direct spread) or iatrogenic peritoneal dissemination (eg, laparoscopic procedures). Imaging findings of peritoneal carcinomatosis include solitary or multiple nodular or rindlike diffuse soft-tissue thickening and fat stranding of the peritoneum, mesentery, or omentum with or without ascites.



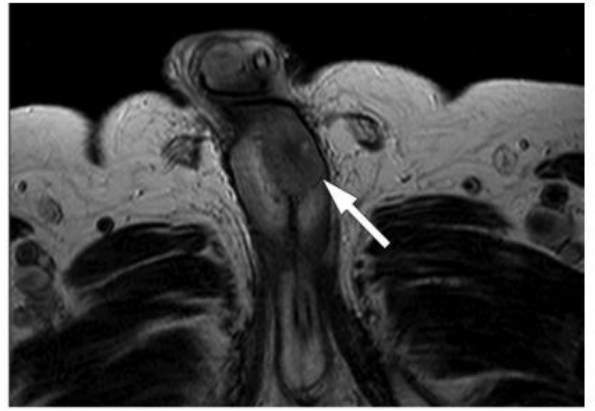
URETERAL METASTASIS

- Upper urinary tract obstruction caused by prostate carcinoma is most commonly due to direct ureteral invasion at the vesicoureteral junction and extrinsic compression by periureteral lymphadenopathy, while true ureteral metastasis from prostate adenocarcinoma is less common.
- . Hydronephrosis is frequently an early indicator. Imaging findings include solitary or multiple enhancing nodules or masses with upstream ureteral dilatation. Retrograde pyelography can show stricture of the ureter. Differential diagnoses include urothelial carcinoma and metastases from other primary tumors (eg, breast or stomach).



PENILE METASTASIS

- Earlier studies showed bladder (29%) and prostate (23%) cancers to be the most frequent primary tumors causing penile metastasis. The most likely route of spread to the penis is retrograde venous transport because there is communication between the pelvic venous plexuses and the penile dorsal venous system.
- At MRI, penile metastasis typically appears hypointense on both T1- and T2-weighted images, with enhancement after injection of gadolinium contrast material and restricted diffusion.
- Differential diagnoses include corporeal thrombosis or hematoma, chancre, tuberculosis, and nonspecific inflammatory lesions.



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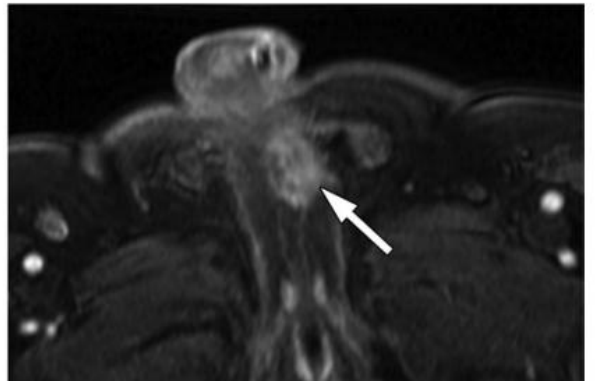
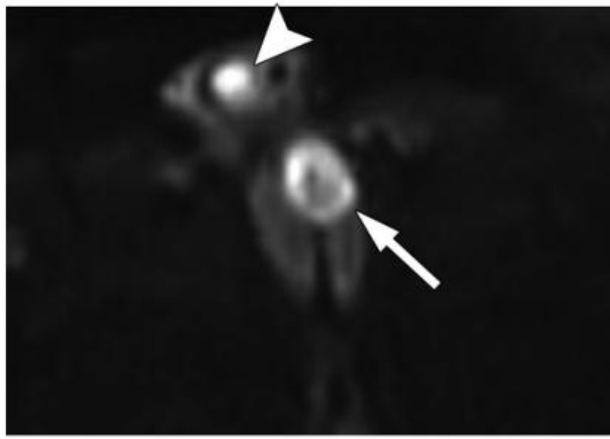
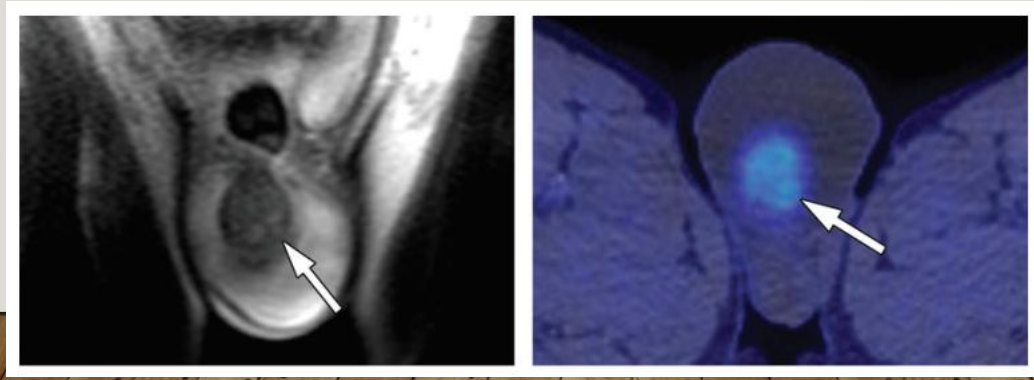




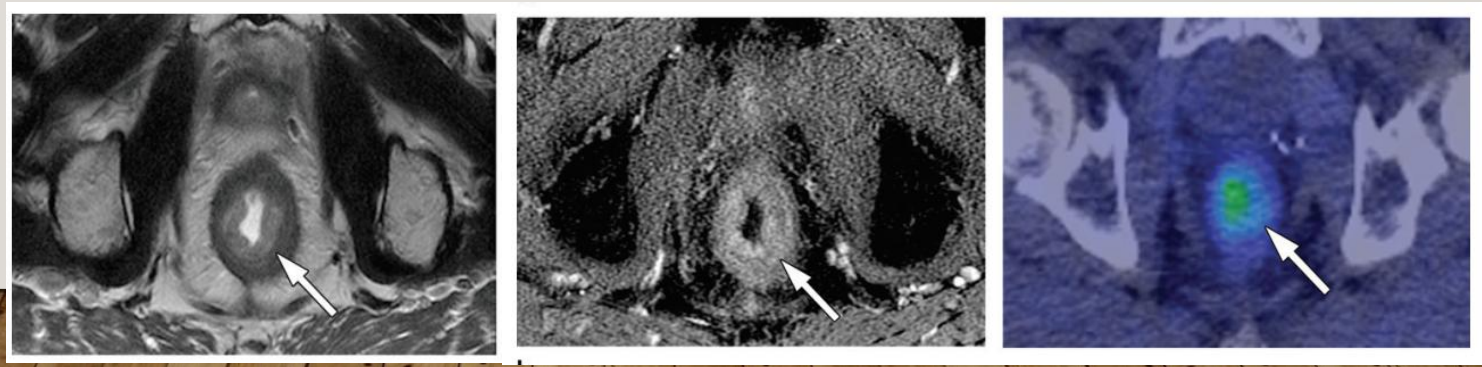
TESTICULAR METASTASIS

- In a series of 26 patients with testicular metastases, the most common primary malignancy was prostate cancer (43%), followed by cancer of the colon (15%), kidney (15%), bladder (12%), or lung (7%).
- Involvement of the prostatic urethra in prostate cancer increases the risk of testicular metastasis.
- Findings of US and other cross-sectional imaging studies include solitary or multiple solid or cystic intratesticular masses. The differential diagnosis includes lymphoma and metastases from other primary tumors.



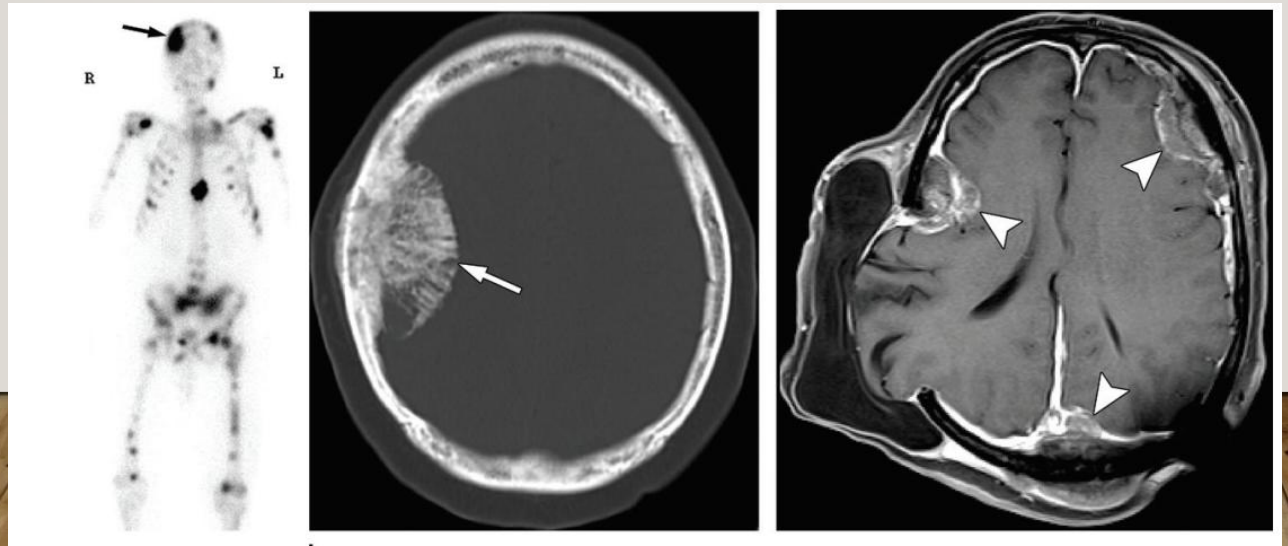
RECTAL METASTASIS

- The low frequency of rectal involvement from prostate cancer, given the anatomic proximity of the two organs, has been considered to be due to the Denonvilliers fascia acting as a barrier to local spread.
- Rectosigmoid involvement has been categorized into the following patterns: type 1, anterior rectal mass (32%); type 2, annular rectal stricture (45%); type 3, ulcerating anterior rectal mass (20%); and type 4, separate metastasis to rectosigmoid (4%). Imaging findings include a rectal mass or diffuse thickening of the rectal wall.
- Histologic confirmation is required to differentiate rectal metastasis from a second primary rectal cancer.



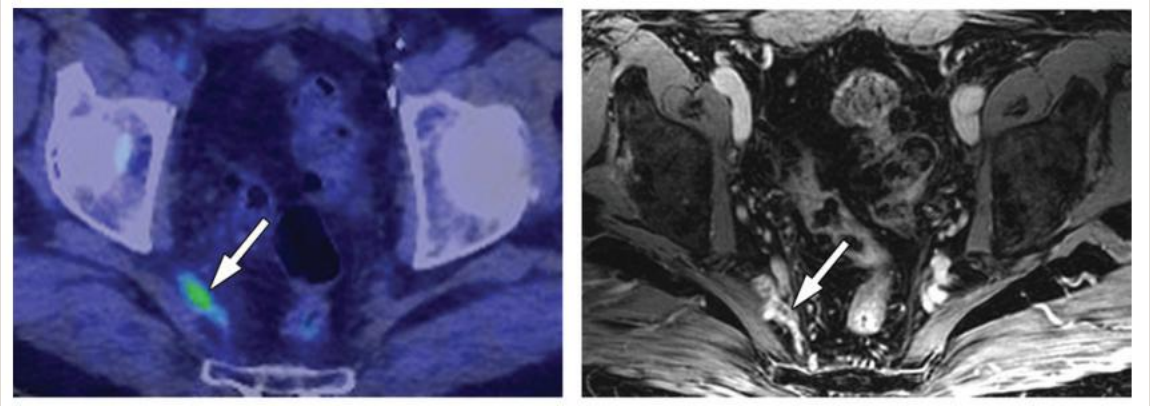
LEPTOMENINGEAL METASTASIS

- In an autopsy study of metastatic prostate cancer, meningeal metastasis (5.9%) was more prevalent than brain metastasis (1.6.
- Direct extension from skull metastasis is the most common mode of spread.
- Imaging findings include solitary or multiple masses, diffuse dural involvement with or without metastasis of the overlying skull, intratumoral or subdural hemorrhage and brain invasion. The differential diagnosis includes meningioma and subdural hematoma



PERINEURAL INVASION BY RECURRENT PROSTATE CANCER

- Prostate cancer occasionally results in lumbosacral plexopathy as the result of perineural extension. Perineural invasion slowly progresses over time after prostatectomy and may be clinically subtle or silent. This can be clinically misdiagnosed as post–radiation therapy neuritis. MRI and molecular PET/CT or PET/MRI may play a complementary role in diagnosing perineural tumor spread



CONCLUSION

- Recurrent and metastatic prostate cancer is a heterogeneous disease with diverse clinical and imaging manifestations. With continued advancement in imaging technologies, proper utilization of more capable modalities allows us to provide earlier and more accurate diagnosis, facilitating appropriate individualized management of patients.


Thank you!