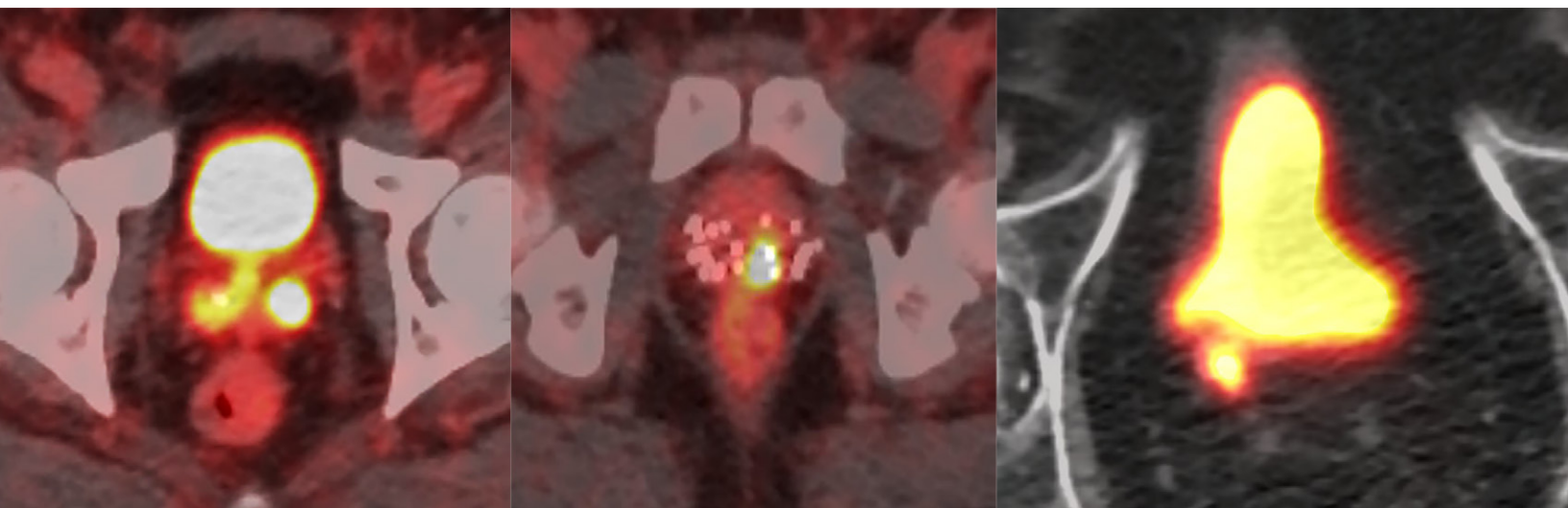


MRI and PSMA PET/CT of Biochemical Recurrence of Prostate Cancer

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Prostate cancer may recur several years after definitive treatment, such as prostatectomy or radiation therapy. A rise in serum prostate-specific antigen (PSA) level is the first sign of disease recurrence, and this is termed *biochemical recurrence*. Patients with biochemical recurrence have worse survival outcomes. Radiologic localization of recurrent disease helps in directing patient management, which may vary from active surveillance to salvage radiation therapy, androgen-deprivation therapy, or other forms of systemic and local therapy. The likelihood of detecting the site of recurrence increases with higher serum PSA level. MRI provides optimal diagnostic performance for evaluation of the prostatectomy bed. Prostate-specific membrane antigen (PSMA) PET radiotracers currently approved by the U.S. Food and Drug Administration demonstrate physiologic urinary excretion, which can obscure recurrence at the vesicourethral junction. However, MRI and PSMA PET/CT have comparable diagnostic performance for evaluation of local recurrence after external-beam radiation therapy or brachytherapy. PSMA PET/CT outperforms MRI in identifying recurrence involving the lymph nodes and bones. Caveats for use of both PSMA PET/CT and MRI do exist and may cause false-positive or false-negative results. Hence, these techniques have complementary roles and should be interpreted in conjunction with each other, taking the patient history and results of any additional prior imaging studies into account. Novel PSMA agents at various stages of investigation are being developed, and preliminary data show promising results; these agents may revolutionize the landscape of prostate cancer recurrence imaging in the future.

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Introduction

Prostate cancer is the most common cancer in men, having an annual incidence of 268 490 and causing 34 500 annual deaths in the United States (1). Prostate cancer is a heterogeneous entity, with the majority of cases being indolent, but rapidly progressive disease occurs in a minority of men (2). Management algorithms for this disease take into account several factors, which include the patient's age, life expectancy, disease stage,

and risk group. In general, surgery is preferred in younger patients with longer life expectancy and organ-confined clinically significant prostate cancer, whereas radiation therapy is preferred in older patients with shorter life expectancy and extraprostatic extension (3,4).

Prostate cancer recurs in up to 15%–40% of patients after radical prostatectomy or radiation therapy, with a median time to recurrence of 24–39 months (2,5–10). Increasing



Quiz questions for this article are available through the [Online Learning Center](#).

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Abbreviations: ADC = apparent diffusion coefficient, DWI = diffusion-weighted imaging, FDA = U.S. Food and Drug Administration, MIP = maximum intensity projection, PI-RADS = Prostate Imaging Reporting and Data System, PSA = prostate-specific antigen, PSMA = prostate-specific membrane antigen

TEACHING POINTS

- The most common site of recurrence after surgery is the prostatectomy bed, and this is identified in 39%–71% of pelvic MRI studies. Recurrence in the prostatectomy bed may occur at the urethrovesical anastomosis (most common site), perivesical fat planes, bladder neck, periurethral region, or penile bulb or within a retained seminal vesicle.
- Dynamic postcontrast imaging is the dominant MRI sequence for detection of local recurrence after prostatectomy, and it has better diagnostic accuracy, enables detection of smaller recurrences, and allows differentiation of true recurrence from benign mimics and equivocal lesions.
- Recurrent cancer occurs at the same site as the irradiated primary tumor in 89%–100% of cases and has a median diameter of about 1 cm. Recurrence at the seminal vesicle is common, occurring in 16%–39% of cases, whereas extraprostatic extension may occur in up to 42% of patients.
- PSMA PET/CT is superior to MRI in detection of lymph node involvement. In addition, it allows identification of unusual sites of lymph node involvement within the pelvis (eg, mesorectal lymph nodes) as well as extrapelvic nodal disease.
- PSMA PET/CT outperforms pelvic MRI and whole-body MRI in evaluation of osseous or visceral recurrence.

prostate-specific antigen (PSA) level is the first indicator of recurrent disease, and this is termed *biochemical recurrence*. Biochemical recurrence earlier than 24–36 months is associated with higher cancer-specific mortality (5,7).

The definition of biochemical recurrence differs according to the treatment modality (prostatectomy vs radiation therapy):

1. For patients who underwent radical prostatectomy, the serum PSA level is expected to become undetectable in a few weeks. Biochemical recurrence is defined as a serum PSA level greater than or equal to 0.2 ng/mL (≥ 0.2 $\mu\text{g/L}$) confirmed in two separate measurements (11). *Persistent disease* is the term used when an undetectable serum PSA level is not achieved after surgery; this may be secondary to local residual disease or unidentified metastatic deposits. Adjuvant radiation therapy or androgen-deprivation therapy is indicated for these patients (4).

2. For patients who received radiation therapy (including brachytherapy or external-beam radiation therapy), serum PSA level is expected to fall gradually. The lowest PSA value reached after radiation therapy is termed the *PSA nadir*. *Biochemical recurrence* is defined as an increase of greater than or equal to 2 ng/mL in serum PSA level above the nadir (12). However, recurrence may be considered and additional evaluation (eg, prostate biopsy) may be performed even though the patient has not yet reached the 2-ng/mL threshold, particularly in younger healthier patients and when there is a rapid increase in serum PSA level (4).

Unestablished treatment options (eg, cryotherapy, high-intensity focused US [HIFU], focal laser ablation) currently have no established and validated cutoff serum PSA value to determine recurrence. In general, a persistent increase in serum PSA level in patients who underwent these therapeutic options is suggestive of recurrence (13). Imaging appearances after these interventions are outside the scope of this article.

The *bounce phenomenon* is defined as a minimal transient rise in serum PSA level at follow-up after radiation therapy. Although there is no definite threshold at which the bounce phenomenon is defined, proposed thresholds for the bounce phenomenon are less than the 2-ng/mL threshold for biochemical recurrence (9,14). The bounce phenomenon occurs earlier than biochemical recurrence, with a median time to rise in PSA level of 16–20 months compared with 34 months for biochemical recurrence (9,14). More than one instance of the bounce phenomenon may occur during patient follow-up (14).

Several factors allow prediction of the site of recurrence with moderate accuracy (80%). Local recurrence is expected when the rise in PSA level occurs greater than 3 years after prostatectomy, PSA level doubling time is greater than 11 months, Gleason score is less than 7, and disease stage is pT3a pN0 or pTx with positive surgical margins (R1). Similarly, systemic recurrence after prostatectomy can be predicted when the rise in PSA level occurs less than 1 year after surgery, PSA level doubling time is 4–6 months, Gleason score is greater than or equal to 8, and disease stage is pT3b or pTx pN1 (15).

A radiologically identifiable site of recurrence affects patient management and is used with other factors (eg, age, comorbidities, life expectancy, PSA level, and PSA level doubling time) to choose the optimal treatment strategy. For patients who had undergone prostatectomy, identifying the site of recurrence is an indication to offer treatment with salvage radiation therapy with or without androgen-deprivation therapy, whereas patients without an identifiable site of recurrence may be observed or may be treated (4). Similarly, for patients with biochemical recurrence after radiation therapy, treatment algorithms tend to recommend additional local therapy or surgical options when there is a radiologically identifiable site of disease, whereas similar patients with negative results at imaging and prostate biopsy may be managed with observation or androgen-deprivation therapy (4).

When distant metastases are identified, systemic therapy options (eg, androgen-deprivation therapy for castration-sensitive prostate cancer) are generally preferred. Radiation therapy may be considered in the setting of metastatic disease for lesions involving weight-bearing bones, pathologic fractures, impending fractures, or nervous structures (eg, spinal cord, neural foramina). Observation without additional therapy may be preferred in patients with short life expectancy (4).

In this article, we review the MRI and prostate-specific membrane antigen (PSMA) PET appearances of recurrent prostate cancer, with emphasis on the limitations and strengths of each modality. In addition, we briefly discuss future directions and hot topics in this field.

Imaging Modalities

MR Imaging

Multiparametric MRI has high spatial resolution and superior tissue contrast resolution, which allow it to be the test of choice for imaging of local recurrence after prostatectomy (4). Multiparametric pelvic MRI protocols typically include small-field-of-view T2-weighted images, diffusion-weighted images, and dynamic contrast-enhanced images for optimal detection of cancer recurrence in the prostate fossa. Additional large-field-of-view T1-weighted, T2-weighted, diffusion-weighted, and delayed postcontrast spoiled gradient-echo images of the pelvis are also obtained, which allow detection and characterization of soft-tissue and bone lesions in the pelvis.

PSMA PET/CT

PSMA PET uses various radiotracers to target PSMA on the surface of prostate cancer cells. Numerous PSMA radiotracers at various stages of investigation have been developed. Currently, the only U.S. Food and Drug Administration (FDA)-approved PSMA radiotracers are fluorine 18 (^{18}F) piflufolastat and gallium 68 (^{68}Ga) PSMA-11 (4). PSMA PET/CT has high sensitivity for detection of prostate cancer metastases. Hence, the current National Comprehensive Cancer Network (NCCN) guidelines consider PSMA PET/CT the preferred test for whole-body staging of bone, soft-tissue, and visceral metastases in patients with biochemical recurrence after surgery or radiation therapy (4).

Expected Imaging Appearances after Prostate Cancer Treatment

Expected Postprostatectomy Appearances

After radical prostatectomy, the urinary bladder descends through the surgical bed to reach the urethra. The bladder neck has a cone-shaped appearance as it descends through the prostatectomy bed. A thin T2-hypointense line may be present at the urethrovesical anastomosis (related to surgical suture material or fibrosis). Fat stranding may be present in the periprostatic or perivesical fat planes. Metallic surgical clips can cause susceptibility artifacts and may have high or low signal intensity at T2-weighted imaging. Diffusion-weighted images are particularly vulnerable to these artifacts and may become severely degraded or nondiagnostic when numerous metallic clips are present in the prostatectomy fossa (16).

The seminal vesicles are typically resected at surgery, but some surgeons may choose to perform seminal vesicle-sparing prostatectomy, in which the seminal vesicles are left in place unilaterally or bilaterally. In addition, the tips of the seminal vesicles may be left behind unintentionally and should not be confused with recurrent cancer. The retained seminal vesicles may maintain their racemose appearance, with high signal intensity at T2-weighted imaging, or they may become small and fibrotic with low T2 signal intensity (17). Although the seminal vesicles do secrete PSA, serum levels typically remain below 0.2 ng/mL, which is the accepted threshold for biochemical recurrence (18).

Residual prostate tissue may be left behind after radical prostatectomy. Although benign prostate tissue at the resec-

tion margins is present in up to one-third of pathology specimens, only up to 3% of patients have identifiable residual tissue at MRI (19,20). The most common sites of residual prostatic parenchyma are the prostatic apex (under the vesicourethral anastomosis), bladder neck, and behind the urinary bladder (19). However, this residual benign tissue is not an independent factor for biochemical recurrence (20).

Lymphoceles may develop in the pelvic sidewall after pelvic lymph node dissection. Lymphoceles have thin walls and typically demonstrate high signal intensity on T2-weighted images without enhancement on postcontrast images (21).

Expected Post–Radiation Therapy (Brachytherapy or External-Beam Radiation Therapy) Appearances

After radiation therapy, the uninvolved prostatic parenchyma demonstrates several changes, including decrease in prostate gland volume, diffuse decrease in T2 signal intensity with loss of zonal differentiation, increase in apparent diffusion coefficient (ADC), and contracted seminal vesicles with low signal intensity at T2-weighted imaging (Fig 1) (22–24).

In addition, radiation therapy may also cause changes in extraprostatic pelvic organs, which include the following: fatty replacement of the bone marrow, causing homogeneous high signal intensity on non-fat-saturated T2-weighted images; edema and fatty atrophy of the pelvic musculature; edema and thickening of the rectal wall; contracted urinary bladder with thickened walls (radiation cystitis); and insufficiency fractures of the pelvic bones, which may manifest as high signal intensity in the bone marrow on fat-saturated T2-weighted images or low *b* value diffusion-weighted images (22,24–26).

As with the uninvolved prostatic parenchyma, the irradiated prostate malignancy also demonstrates gradual changes after treatment, including decrease in size, gradual increase in ADC, decrease in signal intensity at diffusion-weighted imaging (DWI), and decrease in contrast enhancement. Complete resolution of tumor enhancement occurs in 17% of patients 3 months after radiation therapy and 78% of patients 12 months after radiation therapy (27).

Absorbable hydrogel spacers (eg, SpaceOAR [Boston Scientific]) are used to decrease radiation-related rectal toxic effects. This gel-like material creates a space separating the prostate and rectum and is injected under US guidance through a perineal approach. These hydrogels have high signal intensity on T2-weighted images and low signal intensity on T1-weighted images. At CT, some hydrogels demonstrate soft-tissue attenuation, although some newly developed hydrogel formulas demonstrate high attenuation to facilitate visualization at CT. Hydrogel spacers are typically absorbed within 3–6 months after placement (28). The authors have observed cases of abscess formation and hematoma secondary to hydrogel spacer placement.

MRI of Local Recurrence after Radical Prostatectomy

The most common site of recurrence after surgery is the prostatectomy bed, and this is identified in 39%–71% of pelvic MRI studies (29–34). Recurrence in the prostatectomy bed may occur at the urethrovesical anastomosis (most common site),

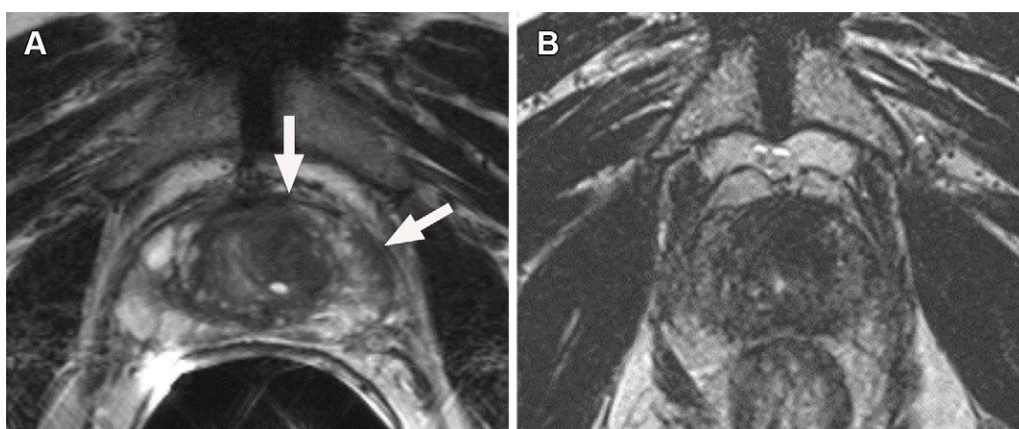


Figure 1. Post–radiation therapy changes in a 62-year-old man with lower urinary tract symptoms and high serum PSA level (11.3 ng/mL). (A) Axial T2-weighted image of the prostate gland shows suspicious transition and peripheral zone lesions (arrows), which were proved to be prostate adenocarcinoma at biopsy. (B) Axial T2-weighted image 12 months after completion of radiation therapy shows expected post–radiation therapy changes, including decrease in prostate volume, diffuse decrease in T2 signal intensity of the prostatic parenchyma, and obscuration or loss of zonal differentiation. Fibrotic changes in the prostatic parenchyma secondary to radiation therapy obscure the irradiated tumors, which are no longer identifiable.

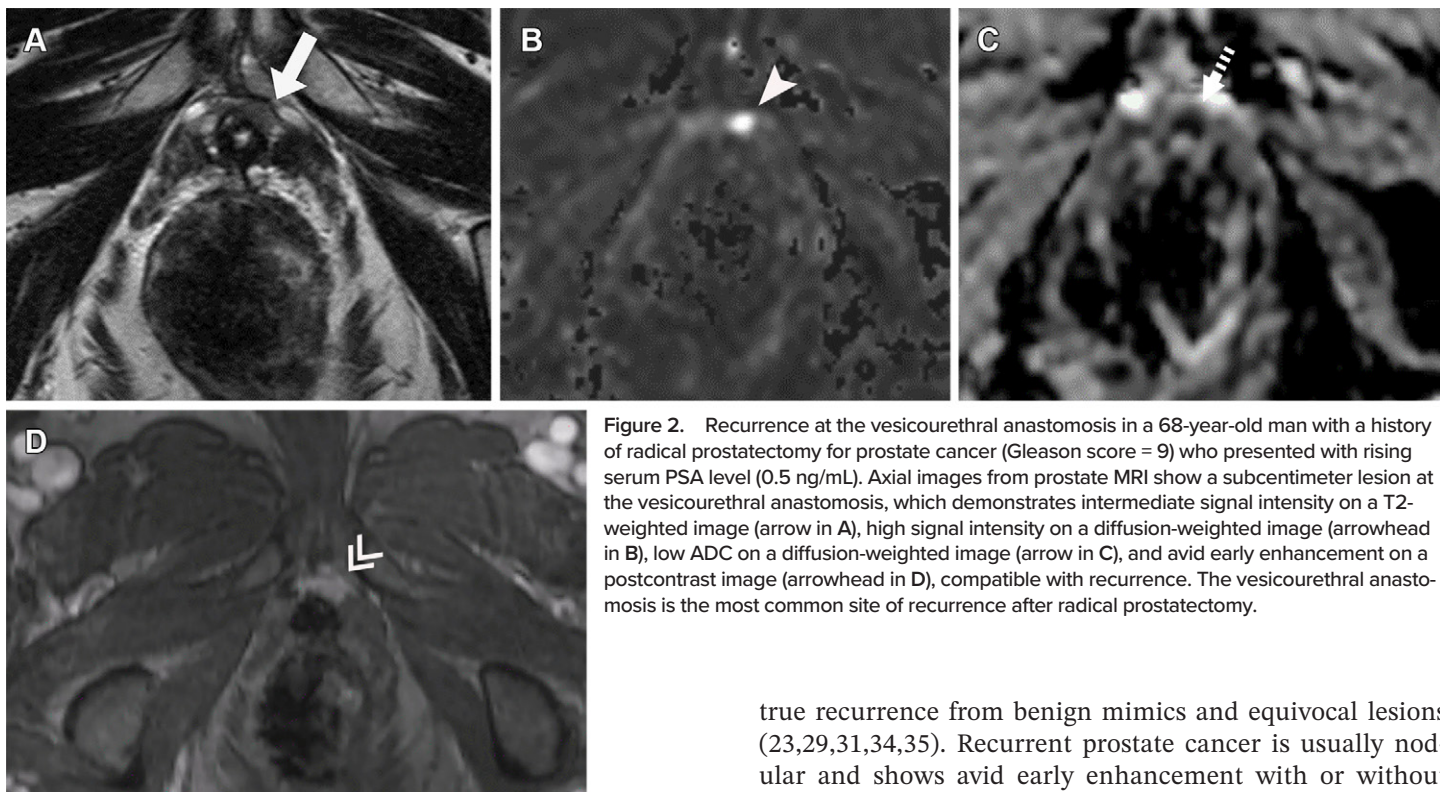


Figure 2. Recurrence at the vesicourethral anastomosis in a 68-year-old man with a history of radical prostatectomy for prostate cancer (Gleason score = 9) who presented with rising serum PSA level (0.5 ng/mL). Axial images from prostate MRI show a subcentimeter lesion at the vesicourethral anastomosis, which demonstrates intermediate signal intensity on a T2-weighted image (arrow in A), high signal intensity on a diffusion-weighted image (arrowhead in B), low ADC on a diffusion-weighted image (arrow in C), and avid early enhancement on a postcontrast image (arrowhead in D), compatible with recurrence. The vesicourethral anastomosis is the most common site of recurrence after radical prostatectomy.

perivesical fat planes, bladder neck, periurethral region, or penile bulb or within a retained seminal vesicle (Figs 2–5) (6,23,32–35). Identification of multiple foci of local recurrence is not uncommon (33). Local recurrence ranges between 3 and 40 mm in size (6,23,30,31,33–35). The probability of identifying local recurrence at MRI is three times higher when serum PSA level is greater than 0.4 ng/mL (34).

Dynamic postcontrast imaging is the dominant MRI sequence for detection of local recurrence after prostatectomy, and it has better diagnostic accuracy, enables detection of smaller recurrences, and allows differentiation of

true recurrence from benign mimics and equivocal lesions (23,29,31,34,35). Recurrent prostate cancer is usually nodular and shows avid early enhancement with or without washout in greater than 90% of cases, whereas weak enhancement is present in about 5% of cases (34). This pattern of early enhancement helps rule out recurrence in equivocal lesions that may mimic recurrence with other MRI sequences (fibrotic scar, retained seminal vesicle, and hematoma) (34). Kitajima et al (31) reported that the combination of T2-weighted imaging and DWI allowed detection of only 25% of subcentimeter (<10 mm) recurrences compared with the combination of all three sequences (dynamic postcontrast imaging, DWI, and T2-weighted imaging).

Recurrent prostate cancer shows intermediate to high signal intensity on T2-weighted images, restricted diffusion on diffusion-weighted images, and corresponding low signal intensity

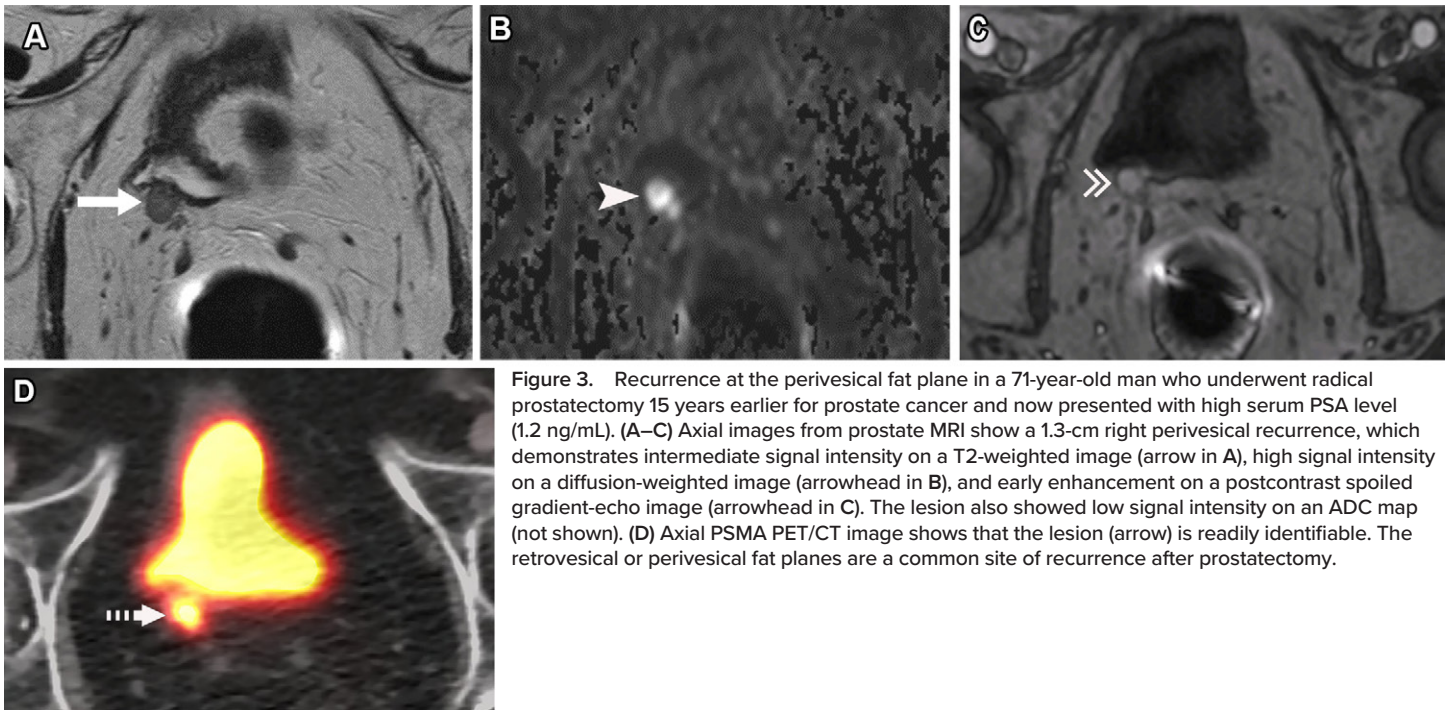


Figure 3. Recurrence at the perivesical fat plane in a 71-year-old man who underwent radical prostatectomy 15 years earlier for prostate cancer and now presented with high serum PSA level (1.2 ng/mL). (A–C) Axial images from prostate MRI show a 1.3-cm right perivesical recurrence, which demonstrates intermediate signal intensity on a T2-weighted image (arrow in A), high signal intensity on a diffusion-weighted image (arrowhead in B), and early enhancement on a postcontrast spoiled gradient-echo image (arrowhead in C). The lesion also showed low signal intensity on an ADC map (not shown). (D) Axial PSMA PET/CT image shows that the lesion (arrow) is readily identifiable. The retrovesical or perivesical fat planes are a common site of recurrence after prostatectomy.

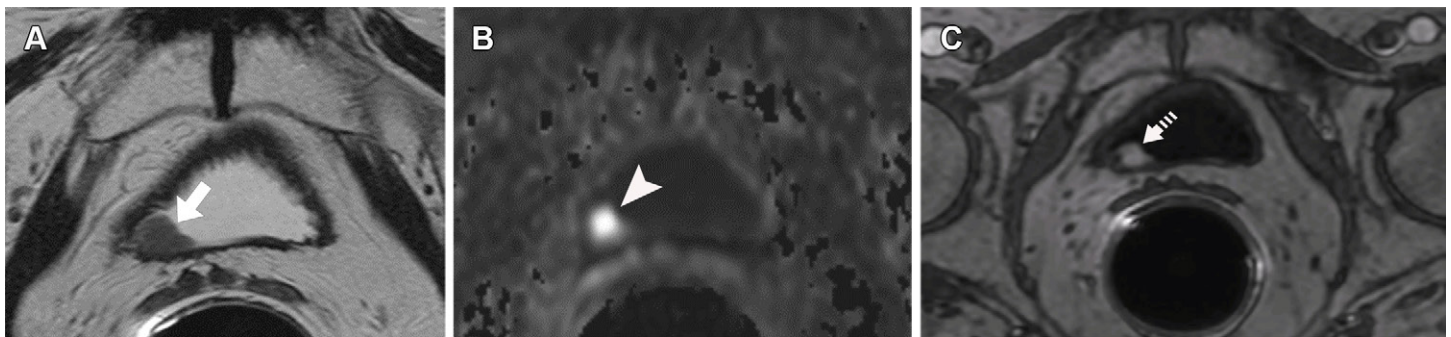


Figure 4. Recurrence at the intraluminal bladder in a 73-year-old man who underwent prostatectomy 17 years earlier for prostate adenocarcinoma (Gleason score = 7) and now presented with high serum PSA level (1.1 ng/mL). Axial MR images show a 1.2-cm intraluminal bladder lesion, which demonstrates intermediate signal intensity on a T2-weighted image (arrow in A), high signal intensity on a diffusion-weighted image (arrowhead in B) with corresponding low signal intensity on an ADC map (not shown), and early enhancement on a postcontrast spoiled gradient-echo image (arrowhead in C). The lesion was initially suspected to be a primary bladder malignancy, but cystoscopic biopsy demonstrated recurrent prostate cancer. Lesions within the bladder may be obscured at PSMA PET due to the high physiologic urinary excretion of currently FDA-approved PSMA radiotracers.

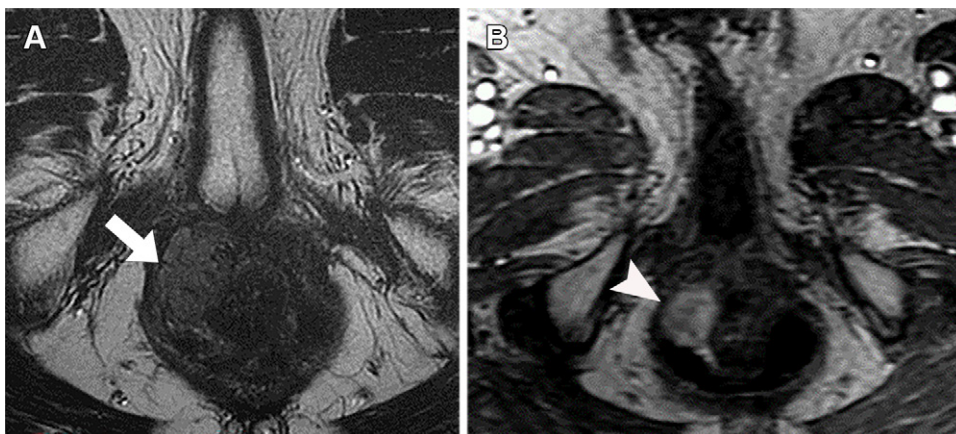


Figure 5. Recurrence at the intersphincteric space in a 66-year-old man who underwent radical prostatectomy for prostate adenocarcinoma (Gleason score = 8) 3 years earlier. Positive surgical margins were present at the prostate apex. The patient now presented with a serum PSA level of 5.2 ng/mL. Axial MR images show a 2.9-cm recurrent lesion in the right intersphincteric space, which demonstrates intermediate signal intensity on a T2-weighted image (arrow in A) and avid early enhancement on a postcontrast spoiled gradient-echo image (arrowhead in B). This case shows that prostate cancer involving the apex may recur in the intersphincteric space or penile bulb.

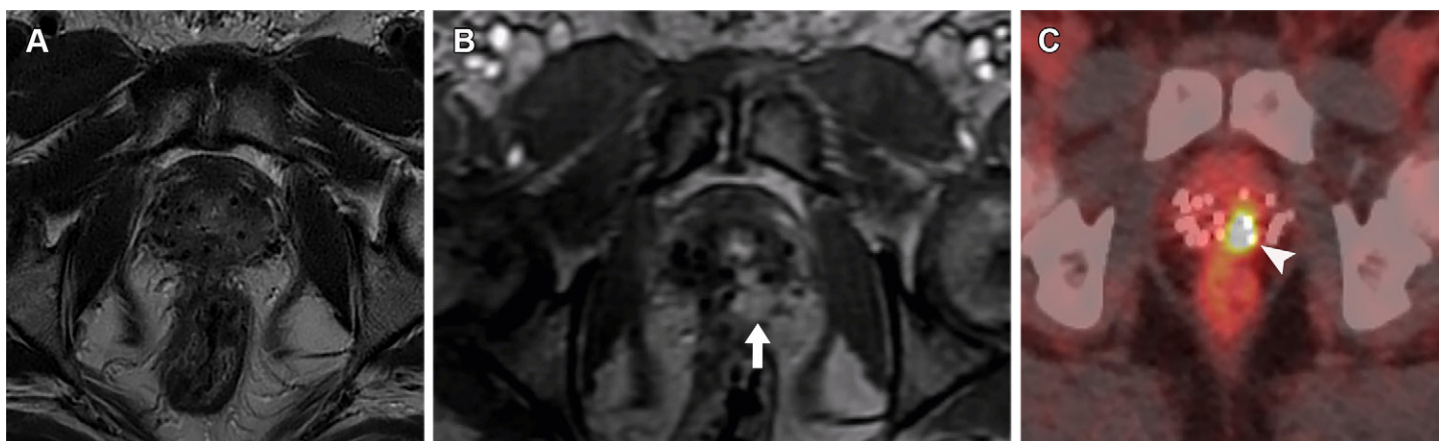


Figure 6. Intraparenchymal recurrence in a 68-year-old man with elevated serum PSA level (7.8 ng/mL) 10 years after brachytherapy. (A) Axial T2-weighted image shows diffuse low signal intensity and obscuration of zonal differentiation secondary to radiation treatment without an identifiable recurrent mass. Note the punctate hypointense brachytherapy seeds. Diffusion-weighted images (not shown) were nondiagnostic due to severe susceptibility artifacts from the brachytherapy seeds. (B) Axial postcontrast spoiled gradient-echo image shows a 1.5-cm early enhancing peripheral zone lesion (arrow) in the left apex, in keeping with an intraparenchymal recurrence. (C) Axial PSMA PET/CT image shows avid uptake (arrowhead) in the recurrent lesion, whereas the uninvolved adjacent prostatic parenchyma shows low background radiotracer activity.

on ADC maps. However, many foci of disease recurrence do not show these appearances. Kwon et al (30) reported that DWI yielded a sensitivity of 97%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 89% for detection of foci greater than or equal to 1 cm in the prostatectomy fossa. However, the sensitivity for lesions smaller than 1 cm was 44%. Hence, DWI is not a reliable tool for identification of subcentimeter local recurrences.

In another study, lower ADC correlated with higher grade at histologic evaluation, and benign tissue had higher ADC ranging between 1.3 and 1.7 mm²/sec (35). In a recent study with four readers, dynamic postcontrast imaging yielded the best diagnostic performance with the highest area under the receiver operating characteristic (ROC) curve (AUC) of 0.81–0.88, followed by T2-weighted imaging (AUC = 0.67–0.88) and DWI (AUC = 0.64–0.77) (29).

Verification of local recurrence of prostate cancer is challenging because many lesions identified at MRI are too small to detect with transrectal US (TRUS) and hence too small to biopsy. In a large study that included 262 patients, TRUS-guided histologic sampling could not be performed in smaller lesions of 4–8 mm but was possible in larger foci of recurrent disease of 9–15 mm (35). Hence, composite reference standards for diagnosing true-positive local recurrence of prostate cancer after prostatectomy or radiation therapy are used.

These composite reference standards include (a) positive biopsy results, (b) decrease in size of the suspected recurrence or decrease in serum PSA level after treatment (prostate fossa salvage radiation therapy or systemic therapy) at long-term (>24 month) follow-up (provided the patient has no other foci of metastatic disease at other nuclear imaging modalities performed at the time of MRI), and (c) increase in size of the suspected lesion at follow-up imaging (eg, MRI or PSMA PET/CT) at greater than 12 months (29).

Criteria for defining true-negative local recurrence of prostate cancer include (a) negative biopsy results and (b) resolution or absence of progression of the suspected focus without

therapy at long-term (12-month) follow-up imaging (eg, MRI or PSMA PET/CT) without increasing serum PSA level for greater than 24 months (29).

MRI of Local Recurrence after Prostate Radiation Therapy (External-Beam Radiation Therapy or Brachytherapy)

After external-beam radiation therapy, local recurrence is identified in 29%–86% of MRI examinations in patients with biochemical recurrence (29,36–40). The median time to recurrence after radiation therapy ranges from 5 to 194 months (29,37–42). The median serum PSA level at the time of recurrence varies from 1.9 to 4.5 ng/mL (range, 0.1–41.8 ng/mL) (22,29,37–39,41–43).

Recurrent cancer occurs at the same site as the irradiated primary tumor in 89%–100% of cases and has a median diameter of about 1 cm (23,43,44). Recurrence at the seminal vesicle is common, occurring in 16%–39% of cases, whereas extraprostatic extension may occur in up to 42% of patients (4,22,36,45,46). Multifocal local recurrence may be encountered at MRI but is more frequent at prostate biopsy and in salvage prostatectomy specimens (23,43).

At MRI, recurrent prostate cancer after radiation therapy typically has lower signal intensity on T2-weighted images compared with the adjacent prostatic parenchyma, high signal intensity on diffusion-weighted images, corresponding low signal intensity on ADC maps, and early enhancement on dynamic postcontrast imaging (Figs 6, 7) (29,41).

Dynamic postcontrast imaging and DWI provide significantly better sensitivity, specificity, and diagnostic accuracy compared with T2-weighted imaging alone (23,36–38,42). However, most investigators reported no significant improvement in the diagnostic performance of dynamic postcontrast imaging compared with that of DWI (23,38,41,42). For instance, Roy et al (23) reported sensitivity of 72% for T2-weighted imaging, 97% for DWI, 94% for dynamic postcontrast imaging, and 100% for the combination of all three sequences.

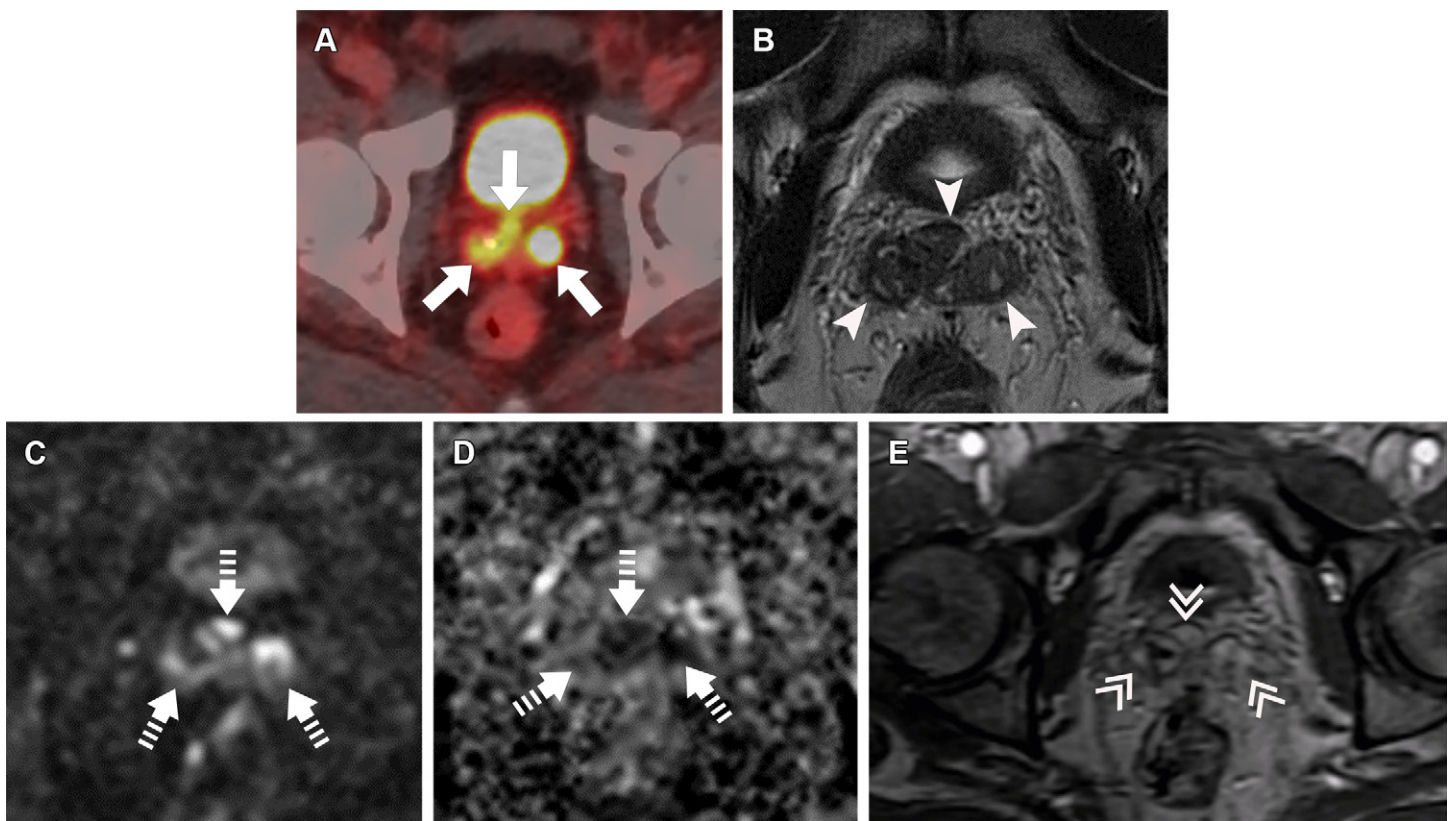


Figure 7. Recurrence in bilateral seminal vesicles and the vas deferens in a 63-year-old man with a history of prostate adenocarcinoma (Gleason score = 4 + 4) treated with brachytherapy 10 years earlier who now presented with high serum PSA level (7.8 ng/mL). (A) Axial PSMA PET/CT image shows increased radiotracer uptake (arrows) in bilateral seminal vesicles as well as in the vas deferens, consistent with disease recurrence. (B–E) Axial MR images show corresponding recurrent malignancy, which demonstrates intermediate signal intensity on a T2-weighted image (arrowheads in B), high signal intensity on a diffusion-weighted image (arrows in C), low signal intensity on an ADC map (arrows in D), and early enhancement on a postcontrast spoiled gradient-echo image (arrowheads in E). The seminal vesicle is a common site of recurrence after radiation therapy.

In another study with four readers, Pecoraro et al (29) reported a pooled area under the receiver operating characteristic (ROC) curve (AUC) of 0.67–0.88 for T2-weighted imaging, 0.64–0.77 for DWI, 0.81–0.88 for contrast-enhanced imaging, and 0.80–0.88 for the combination of all three sequences.

Despite absence of significantly better diagnostic performance of dynamic postcontrast imaging compared with that of DWI, investigators have reported that contrast-enhanced imaging was associated with significantly higher sensitivity in less-experienced readers and improved interreader agreement (41,42). In addition, dynamic postcontrast imaging is less prone to susceptibility artifacts than DWI. In fact, studies comparing these sequences commonly exclude patients with severely degraded diffusion-weighted images. Hence, postcontrast images become of utmost importance in patients with nondiagnostic diffusion-weighted images related to metallic surgical hardware in the hip or pelvis or intraprostatic fiducial markers.

Brachytherapy is a form of radiation therapy in which metallic seeds or pellets containing radioactive material are implanted in the prostatic parenchyma to treat prostate cancer. This form of radiation therapy is preferred in men with low-grade organ-confined cancer with a small-volume prostate. Brachytherapy causes similar imaging changes as external-beam radiation therapy in the prostatic parenchyma and targeted malignancy. However, some forms of metallic

brachytherapy seeds can cause severe susceptibility artifacts. Diffusion-weighted images are particularly vulnerable to susceptibility artifacts and may become severely degraded or nondiagnostic.

Recurrent disease after brachytherapy shows similar imaging appearances as those after external-beam radiation therapy, with diffusion restriction at DWI and focal enhancement at dynamic contrast-enhanced imaging, which have better lesion sensitivity than T2-weighted imaging alone (Fig 6). However, neither DWI nor contrast-enhanced imaging yields a significantly better sensitivity over the other technique (45,47).

PSMA PET/CT for Local Recurrence

Evaluation of the prostatic fossa with PSMA PET/CT is challenging because the currently FDA-approved PSMA radiotracers (^{18}F -piflufolastat and ^{68}Ga -PSMA-11) demonstrate physiologic urinary excretion. Urinary activity can obscure recurrent prostate cancer at the vesicourethral anastomosis or bladder neck or within the urinary bladder lumen. However, recurrence in the periprostatic fat planes, seminal vesicle or vas deferens, or local lymph nodes is readily detectable with PSMA PET/CT (Figs 3, 6, 7).

After radical prostatectomy, MRI yields higher sensitivity for local recurrence of prostate cancer compared with PSMA PET/CT because lesions lying in close proximity to the bladder

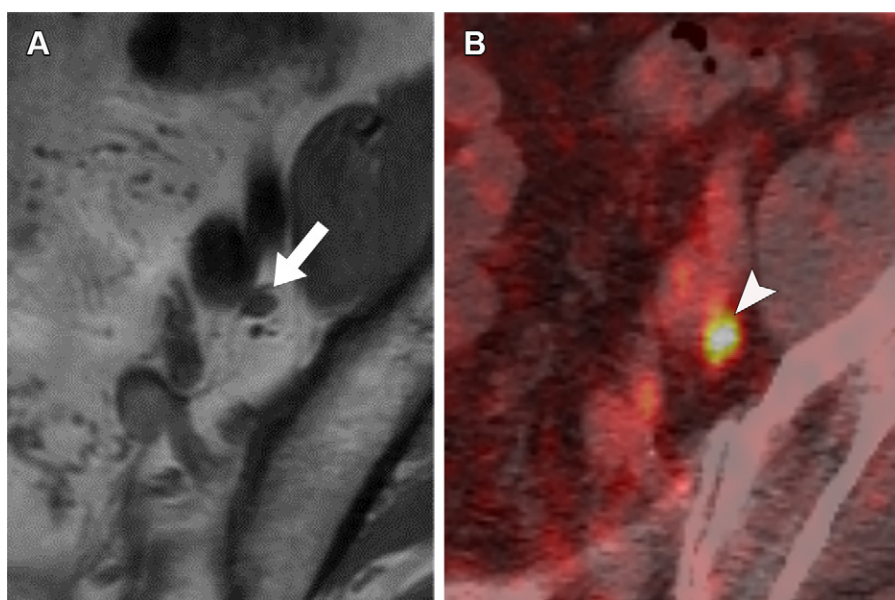


Figure 8. Lymph node recurrence in a 59-year-old man with a history of radical prostatectomy who presented with elevated serum PSA level (0.4 ng/mL). No suspicious lesion was detected within the prostatectomy bed at MRI. (A) Axial T1-weighted image shows a 0.4-cm left obturator lymph node (arrow), which is not suspicious according to size criteria. (B) Axial PSMA PET/CT image shows avid radiotracer uptake (arrowhead) in the lymph node, suggestive of lymph node recurrence. This case highlights the superiority of PSMA PET over cross-sectional imaging modalities (CT or MRI) in detection of small lymph node metastases.

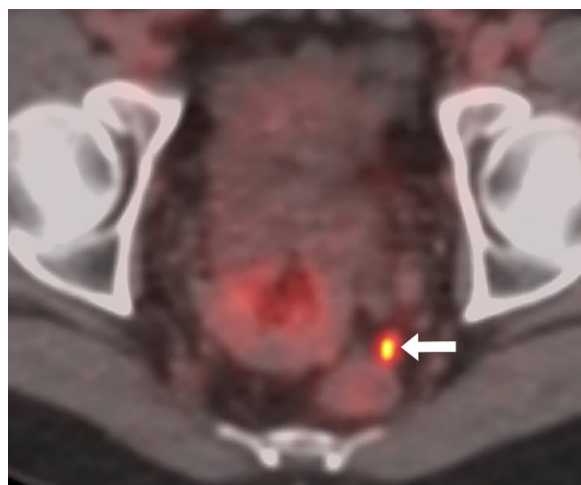


Figure 9. Lymph node recurrence in a 57-year-old man who underwent radical prostatectomy for prostate adenocarcinoma 3 years earlier and now presented with rising serum PSA level (0.3 ng/mL). Axial PSMA PET/CT image shows avid uptake (arrow) in a 0.5-cm mesorectal lymph node. Recurrent malignancy was confirmed at US-guided transrectal biopsy.

(eg, at the urethrovesical anastomosis) are obscured by the urinary activity of PSMA (48,49). Freitag et al (48) reported that only one-half of local recurrences seen at MRI after prostatectomy were identifiable at PSMA PET. In the same study, proximity of the recurrent lesion to the bladder was significantly associated with false-negative PSMA PET results, whereas the size of the recurrent lesion was not associated with false-negative PSMA PET results (48). In another study, MRI had better diagnostic performance for local recurrence than PSMA PET/CT, with sensitivity of 91% (vs 64%), specificity of 95% (vs 74%), and accuracy of 92% (vs 78%) (49).

A few interventions have been suggested to decrease physiologic urinary PSMA activity and enhance visualization of recurrent cancer in the prostatectomy bed. These include early acquisition of PSMA PET/CT images (as early as 6 minutes after radiotracer injection), administration of intravenous di-

uretics (eg, furosemide), and asking the patient to void just before obtaining the PET images (50).

After external-beam radiation therapy or brachytherapy, the prostate gland remains in place, and local recurrence within the prostatic parenchyma or seminal vesicles is more remote from the physiologic urinary activity of PSMA. Hence, recurrent tumor demonstrating focal PSMA uptake is readily identifiable, with good tissue contrast relative to the nonmalignant irradiated prostatic parenchyma (Fig 6). For instance, in a study that evaluated biochemical recurrence after brachytherapy, 53% of patients had local recurrence within the irradiated prostate, all of which were identifiable at PSMA PET/CT and 88% of which were identifiable at pelvic MRI (46). In the same study, recurrence involving the seminal vesicles was present in 34% of patients, all of which were identifiable at PSMA PET/CT and 82% of which were identifiable at MRI (46). A similar study of patients who underwent external-beam radiation therapy reported similar results, with 68% of patients demonstrating local recurrence at PSMA PET/CT compared with 63% of patients demonstrating local recurrence at MRI (51).

Lymph Node Recurrence

The second most common site of prostate cancer recurrence is the lymph nodes, and the most involved nodes are regional lymphatic chains (internal or external iliac, presacral, and obturator lymph nodes) (46,51–53). Extrapelvic lymph node metastases occur in up to 3%–18% of cases, but isolated extrapelvic nodal involvement is uncommon (46,49,51,53,54).

PSMA PET/CT is superior to MRI in detection of lymph node involvement (46,49,51,52,55). In addition, it allows identification of unusual sites of lymph node involvement within the pelvis (eg, mesorectal lymph nodes) as well as extrapelvic nodal disease (Figs 8–10) (51–54,56). For instance, in a study that included patients who underwent salvage pelvic lymphadenectomy for recurrent prostate cancer, PSMA PET/CT and/or PSMA PET/MRI allowed correct identification of lymph node involvement in 78% of the resected lymphatic chains compared with 27% for cross-sectional imaging. In addition,



Figure 10. Local and distant lymph node recurrence in a 71-year-old man who underwent radical prostatectomy for prostate adenocarcinoma 5 years earlier and now presented with rising serum PSA level (1.1 ng/mL). Coronal maximum intensity projection (MIP) PSMA PET image shows avid uptake in recurrent lesions in the prostatectomy bed and perivesical fat plane (arrowheads), as well as in several retroperitoneal lymph nodes and a left supraclavicular lymph node (arrows).

PSMA PET/CT and/or PSMA PET/MRI allowed identification of smaller lymph node deposits (mean, $8.3 \text{ mm} \pm 4.3$ [range, 4–25 mm] for PET vs $13.0 \text{ mm} \pm 4.9$ [range, 8–25 mm] for cross-sectional imaging). False-negative lymph nodes at PSMA PET/CT and/or PSMA PET/MRI had a mean size of 4.7 mm (range, 0.5–11 mm) (52).

Lymph node evaluation at MRI has low sensitivity and relies on size and morphologic features. Although the Prostate Imaging Reporting and Data System (PI-RADS) 2.1 guidelines suggest a short-axis threshold of 8 mm, there are no universally accepted criteria for defining suspicious pelvic lymph nodes, and very small lymph nodes can still harbor micrometastases. On the other hand, enlarged lymph nodes may be malignant or reactive. For instance, in a study that included patients with recurrent prostate cancer who underwent salvage surgery with pelvic lymphadenectomy, only one-third of suspicious lymph nodes seen at preoperative MRI were malignant at resection, whereas 88% of involved lymph nodes were missed at preoperative MRI (all of which measured $<5 \text{ mm}$) (22).

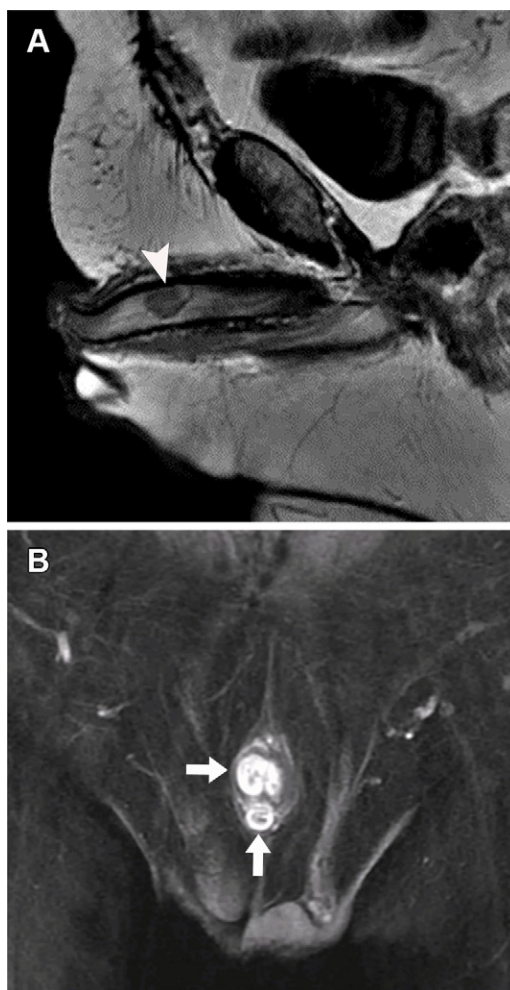


Figure 11. Penile recurrence in a 63-year-old man who presented with elevated serum PSA level (11.3 ng/mL) 9 years after radical prostatectomy. (A) Sagittal T2-weighted image shows a 1.1-cm lesion (arrowhead) in the penile corpus cavernosum. (B) Coronal postcontrast spoiled gradient-echo image shows two additional early-enhancing recurrent tumors (arrows) involving the urethra and right corpus cavernosum. The penis is an uncommon site for metastasis.

Bone or Visceral Recurrence

Osseous structures are the third most common site of prostate cancer recurrence (after local recurrence and lymph node involvement), occurring in 9%–15% of patients (56–58). Soft-tissue or visceral metastases are uncommon, occurring in 1%–9% of patients, and most involve the liver or lungs. Isolated visceral metastases are rare ($<1\%$ of cases) (56,57). PSMA PET/CT outperforms pelvic MRI and whole-body MRI in evaluation of osseous or visceral recurrence (58,59). Metastatic disease involving pelvic organs within the field of view of pelvic MRI (eg, rectum, penis, musculature) is uncommon (Figs 11, 12), but these rare sites should also be scrutinized in addition to the more common locations of recurrence.

Whole-body MRI has a large field of view extending from the skull base to the mid thighs. Typical whole-body MRI sequences include non-fat-saturated T1-weighted imaging, DWI, ADC mapping, short τ inversion recovery (STIR), and spoiled gradient-echo T1-weighted imaging (60). The typical appearance of prostate metastases at MRI includes low signal intensity at T1-weighted imaging, high signal intensity at DWI, and corresponding low signal intensity at ADC mapping. Viable prostate metastases typically have an ADC of $0.7\text{--}1.4 \text{ mm}^2/\text{sec}$, which is higher than that of uninvolved bone marrow ($<0.6\text{--}0.7 \text{ mm}^2/\text{sec}$) (Fig 13) (60).

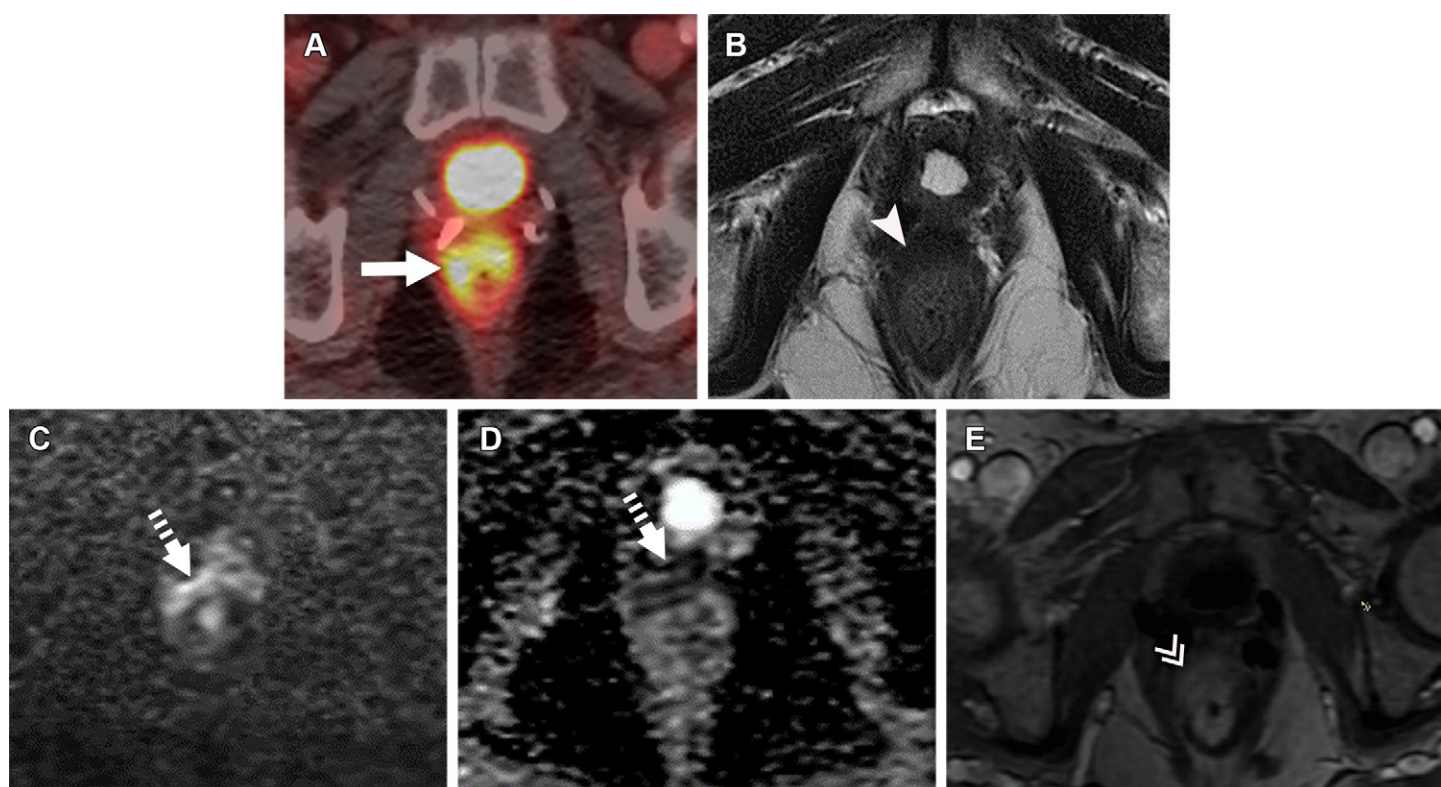


Figure 12. Rectal wall recurrence in a 71-year-old man who presented with high PSA level (9.8 ng/mL) 12 years after prostatectomy. (A) Axial PSMA PET/CT image shows C-shaped radiotracer uptake (arrow) along the anterior rectal wall. (B–E) Axial images from subsequent MRI show a 2.5-cm corresponding recurrent prostate cancer, which demonstrates intermediate signal intensity on a T2-weighted image (arrowhead in B), high signal intensity on a diffusion-weighted image (arrow in C) with corresponding low signal intensity on an ADC map (arrow in D), and early enhancement on a postcontrast spoiled gradient-echo image (arrowhead in E). The rectal wall is an uncommon site for metastasis.

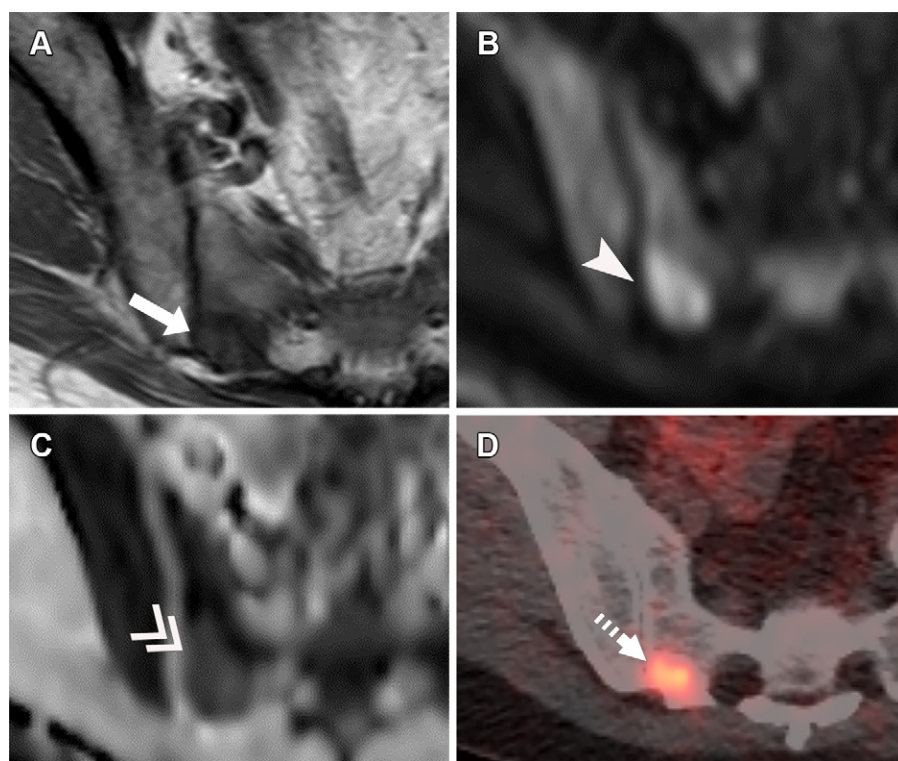


Figure 13. Osseous metastasis in a 60-year-old man with prostate adenocarcinoma (Gleason score = 4 + 4) and biochemical recurrence. (A–C) Axial MR images show a 2.2-cm recurrent osseous lesion in the right hemiacrum, which demonstrates hypointense signal on a T1-weighted image (arrow in A), high signal intensity on a diffusion-weighted image (arrowhead in B), and corresponding low signal intensity on an ADC map (arrowhead in C), in keeping with an osseous metastasis. (D) Axial PSMA PET/CT image shows corresponding high radiotracer uptake (arrow) in the metastasis. Normal bone marrow has lower ADC (<0.6 – 0.7 mm²/sec) than osseous metastases from prostate cancer (ADC = 0.7 – 1.4 mm²/sec), as seen in this example.

Entities Other than Prostate Cancer Associated with Elevated PSMA Uptake That May Cause False-Positive Assessment

Benign entities

Celiac ganglia
 Stellate ganglia
 Granulomatous diseases (eg, sarcoidosis, Wegener granulomatosis, tuberculosis)
 Paget disease of bone
 Fibrous dysplasia
 Healing bone fractures
 Hemangioma (vascular malformation) of the liver, bone, or soft tissues
 Desmoid tumor
 Nodular fasciitis
 Dermatofibroma
 Intramuscular myxoma
 Acrochordon
 Meningioma
 Schwannoma
 Peripheral nerve sheath tumor
 Amyloidosis
 Thyroid follicular adenoma
 Serous cystadenoma of the pancreas
 Adrenal adenoma
 Brain infarction
 Pseudoangiomatous stromal hyperplasia (PASH) of the breast

Malignant entities

Follicular lymphoma
 Multiple myeloma
 Thyroid carcinoma (papillary or follicular)
 Pancreatic neuroendocrine tumor
 Gastrointestinal stromal tumor (GIST)
 Squamous cell carcinoma
 Renal cell carcinoma
 Urothelial carcinoma
 Colorectal carcinoma
 Hepatocellular carcinoma
 Breast carcinoma
 Gastric carcinoma
 Glioblastoma
 Epithelioid hemangioendothelioma of the liver
 Adenoid cystic carcinoma

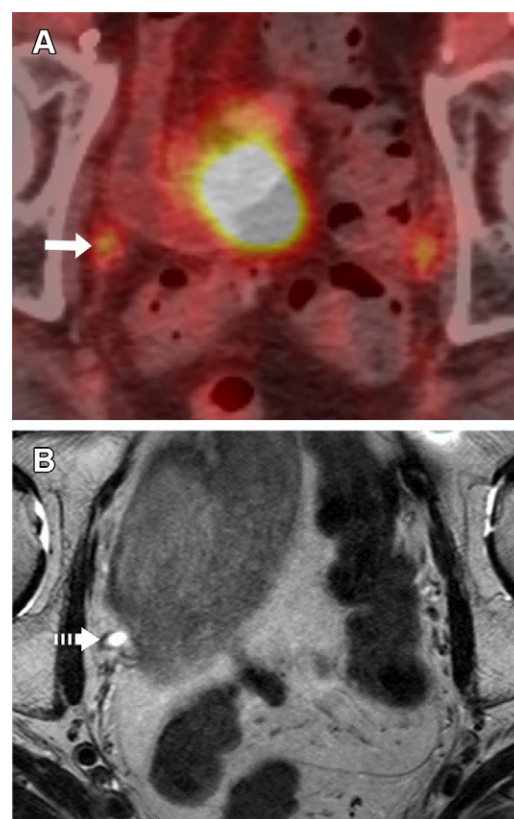


Figure 14. False-positive interpretation in a 65-year-old man with biochemical recurrence. (A) Axial PSMA PET/CT image shows a focus of radiotracer activity (arrow) in the right obturator region, which is suspicious for nodal recurrence. (B) Axial T2-weighted image of this region shows focal dilatation of the right distal ureter (arrow), which accounts for the elevated radiotracer activity noted on the PSMA image. Urinary excretion of PSMA can mimic pelvic sidewall lymph node recurrence and may potentially cause false-positive interpretation.

Despite the extended field of view of whole-body MRI, PSMA PET/CT has significantly better diagnostic performance (58,59). For instance, Zacho et al (58) compared the diagnostic performance of whole-body MRI, ^{68}Ga -PSMA PET/CT, and ^{18}F -sodium fluoride PET/CT and reported better sensitivity for PSMA PET/CT than for MRI (80% vs 25%, respectively).

The diagnostic performance of MRI is limited by several known caveats, which include inability to identify micro-metastases involving nonenlarged lymph nodes, inability to visualize small (<1 cm) lung metastases, and inability to detect small brain metastases in the absence of intravenous contrast material (59,60). In addition, evaluation of the ribs, ster-

num, and skull base may be challenging due to motion and/or susceptibility artifacts (59,60). Osseous metastases may not demonstrate high signal intensity at high-*b*-value DWI when there is sparse infiltration of malignant cells into the bone marrow, when there is dense mineralization of the bone matrix, or when metastases are necrotic (60). On the other hand, several benign entities can exhibit high signal intensity of the bone marrow at DWI, including islands of bone marrow reactivation, vertebral hemangioma, and bone marrow edema secondary to fracture, degenerative processes, infection, or bone infarction (60).

Focal PSMA activity higher than that of the background is considered suspicious for malignancy in the absence of a physiologic or pathologic cause for this uptake (61). Several benign and malignant lesions can cause false-positive PSMA uptake, as outlined in the Table (62). In addition, urinary excretion of PSMA in the ureters may mimic lymph node recurrence, particularly in the pelvis (Fig 14). False-negative PSMA recurrence may occur in up to 3% of cases (63). PSMA-negative prostate cancers showing typical MRI features and avid uptake of other radiotracers (eg, fluciclovine) have been reported (Fig 15) (64).

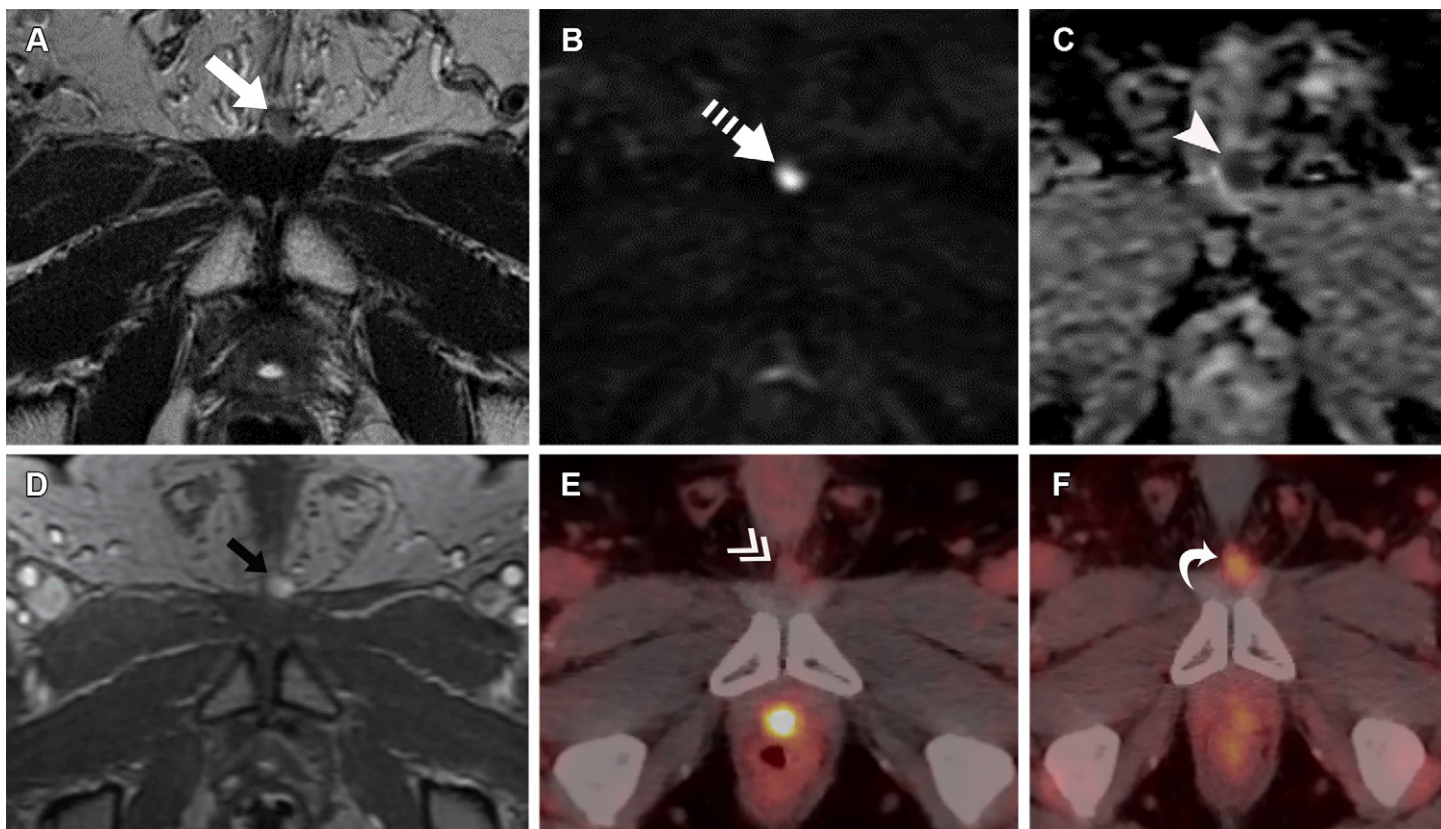


Figure 15. False-negative interpretation in a 71-year-old man who underwent radical prostatectomy 5 years earlier for prostate adenocarcinoma and now presented with elevated serum PSA level (1.3 ng/mL). (A–D) Axial MR images show a 0.6-cm lesion along the anterior pelvic wall, which demonstrates typical features of recurrent prostate cancer, with intermediate signal intensity on a T2-weighted image (arrow in A), high signal intensity on a diffusion-weighted image (arrow in B), low signal intensity on an ADC map (arrowhead in C), and early enhancement on a postcontrast spoiled gradient-echo image (arrow in D). (E) Axial PSMA PET/CT image does not show avid radiotracer uptake in the lesion (arrowhead). (F) Axial fluciclovine PET/CT image does show avid uptake in the lesion (arrow). Percutaneous biopsy demonstrated recurrent prostate adenocarcinoma. Up to 3% of prostate cancers may not demonstrate PSMA uptake, which can result in false-negative interpretation.

Prostate cancer with neuroendocrine differentiation is a rare but important histologic variant of prostate cancer and demonstrates aggressive behavior. This entity rarely develops *de novo*; most cases occur as a result of disease dedifferentiation in patients who received prolonged androgen-deprivation therapy (62). Unlike typical prostate adenocarcinoma, this variant shows little to no PSMA expression and instead may show uptake of radiotracers targeting somatostatin receptors (eg, ^{68}Ga -1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid [DOTA]-octreotate [DOTATATE]) or ^{18}F -fluorodeoxyglucose (^{18}F -FDG) (Fig 16) (62).

Future Directions

Prostate MRI Local Recurrence Reporting (PI-RR) System

Similar to PI-RADS, the prostate MRI local recurrence reporting (PI-RR) system has recently been introduced. It aims to standardize imaging protocols and image acquisition, reduce variation in interpretation, provide specific categories for imaging features seen with different MRI sequences, and offer overall reporting categories (1 to 5) to express the likelihood that MRI findings represent disease recurrence after prostatectomy or radiation therapy (65).

A few studies have evaluated the diagnostic performance of the PI-RR system (29,66). For instance, a recent study with four readers from different institutions using a composite reference standard for diagnosis of recurrent disease reported sensitivity of 59%–83%, specificity of 87%–100%, accuracy of 75%–85%, and interreader agreement coefficient of 0.87 after radical prostatectomy; and sensitivity of 71%–81%, specificity of 74%–93%, accuracy of 77%–88%, and interreader agreement coefficient of 0.87 after radiation therapy (29). These outcomes are in line with the existing literature, and use of this proposed system may facilitate communication with clinicians while minimizing interpretation variability among radiologists.

Novel PSMA PET Agents

Currently FDA-approved PSMA radiotracers demonstrate physiologic urinary excretion, which can obscure recurrence in the prostatic fossa—the most common site of recurrence. Novel PSMA agents (eg, ^{18}F -PSMA-1007 and ^{18}F -radiohybrid [rh] PSMA-7) without urinary excretion were developed and allow better visualization of local disease recurrence (Figs 17, 18) (67,68). For instance, PET/CT with ^{18}F -PSMA-1007 yielded better sensitivity compared with MRI for detection of local recurrence after surgery (91% vs 82%, respectively) (69).

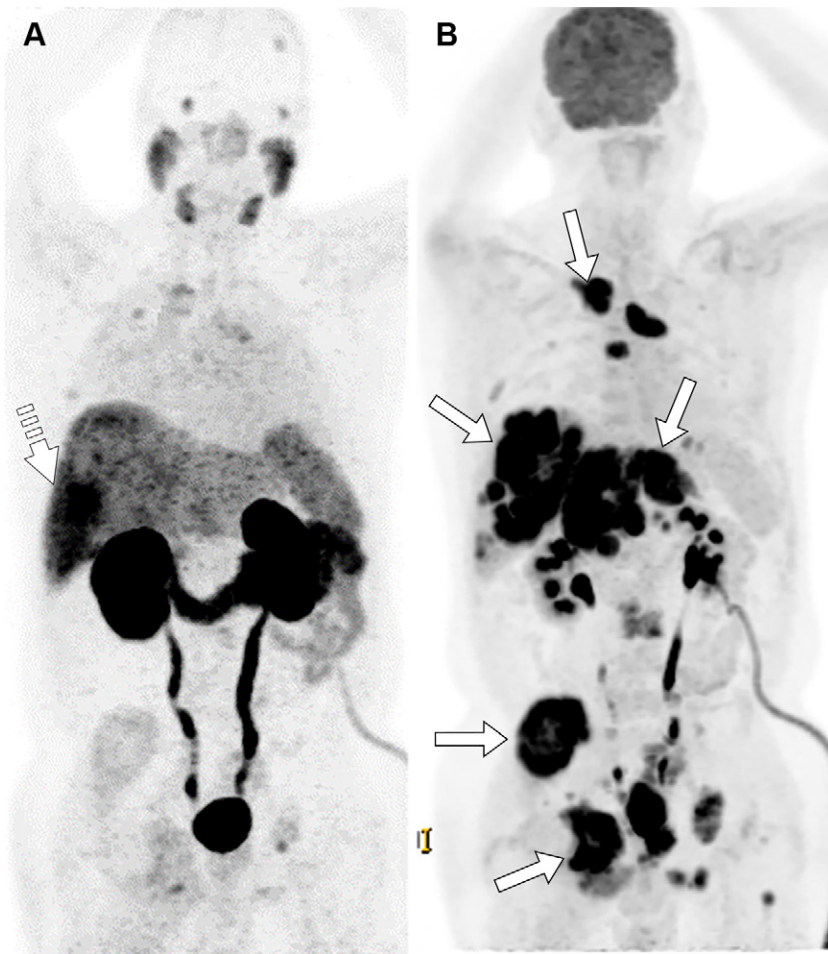


Figure 16. Prostate cancer with neuroendocrine differentiation in a 67-year-old man with castration-resistant prostate adenocarcinoma (serum PSA level = 0.2 ng/mL). (A) Coronal MIP image from PSMA PET shows patchy PSMA uptake (arrow) in a liver metastasis. Several additional PSMA-negative metastases were present on concurrent CT images (not shown). (B) Coronal MIP image from fluorodeoxyglucose (FDG) PET 2 days after the PSMA examination shows avid uptake in several osseous, nodal, and liver metastases (arrows). This example shows that prostate cancer with neuroendocrine differentiation may not demonstrate PSMA uptake, potentially resulting in false-negative interpretation. This entity may occur at presentation (de novo) or more frequently be due to disease dedifferentiation after prolonged androgen-deprivation therapy.

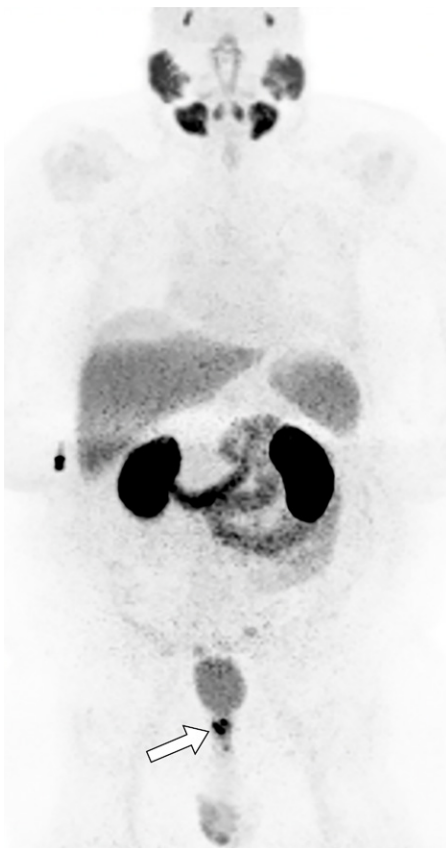


Figure 17. Recurrent lesion in a 69-year-old man with biochemical recurrence after radical prostatectomy for prostate adenocarcinoma (serum PSA level = 0.4 ng/mL). Coronal MIP image from ^{18}F -rhPSMA-7 PET shows avid radiotracer uptake (arrow) in a recurrent lesion at the vesicourethral anastomosis. Note the limited urinary excretion of this novel PSMA radiotracer, which makes recurrence in the vicinity of the urinary bladder more conspicuous.

Studies comparing ^{18}F -rhPSMA-7 PET with MRI for detection of local recurrence after prostatectomy are lacking. However, in one study ^{18}F -rhPSMA-7 was able to demonstrate local recurrence in up to 49% of patients who had undergone radical prostatectomy (70). Hence, novel PSMA PET radiotracers are promising, but preliminary data from these preliminary studies need to be verified in larger cohorts.

Ferumoxtran-10-enhanced MRI

Ferumoxtran-10 is an MRI contrast agent that contains superparamagnetic iron oxide particles. These particles are taken up by macrophages in normal lymph nodes, and due to their susceptibility artifacts, normal lymph nodes have low signal intensity at T2*-weighted MRI. On the other hand, metastatic lymph nodes do not take up this contrast material and have high signal intensity at T2*-weighted MRI (71,72).

A recent study that compared the diagnostic performance of this MRI contrast agent with that of PSMA PET/CT reported that ferumoxtran-10-enhanced MRI allowed detection of significantly more suspicious lymph nodes compared with



Figure 18. Recurrent lesion in a 72-year-old man with biochemical recurrence after radical prostatectomy for prostate adenocarcinoma (serum PSA level = 0.6 ng/mL). Coronal MIP image from ^{18}F -PSMA-1007 PET shows avid radiotracer uptake (arrow) in a recurrent lesion at the vesicourethral anastomosis. Note the absence of urinary excretion of this novel PSMA radiotracer, which makes recurrence in the vicinity of the urinary bladder more conspicuous.

PSMA PET/CT, with 60% of these nodes being detected with ferumoxtran-10-enhanced MRI alone, 11% with PSMA PET/CT alone, and 29% with both modalities. In addition, ferumoxtran-10-enhanced MRI could demonstrate significantly smaller suspicious lymph nodes compared with PSMA PET/CT (73). Despite these promising outcomes, the impact of these findings on patient long-term survival is yet to be determined, and more research is necessary before this imaging technique is adopted into clinical management guidelines.

PSMA-RADS

Similar to PI-RADS, the PSMA Reporting and Data System (PSMA-RADS) is a reporting and data system that has recently been proposed to standardize interpretation, facilitate reporting, and improve communication of PSMA PET/CT findings with clinicians. The PSMA-RADS system is optimized to evaluate extraprostatic findings and expresses the likelihood that they represent true-positive prostate cancer involvement using a five-point scale. On this scale, PSMA-RADS category 1 and 2

lesions or studies represent certainly or almost certainly benign findings, PSMA-RADS category 3 represents equivocal findings that may require additional workup, PSMA-RADS category 4 represents suspicious PSMA uptake without a correlate at anatomic imaging, and PSMA-RADS category 5 represents suspicious PSMA uptake with an anatomic correlate at associated cross-sectional imaging (74,75).

Conclusion

Local recurrence in the prostatic fossa is the most common site of recurrence after prostatectomy and radiation therapy, followed by lymph node and bone recurrence. Multiparametric MRI is the most accurate modality for detection of local recurrence after surgery. MRI and PSMA PET/CT have comparable diagnostic performance for identifying local recurrence after radiation therapy. Lymph node, bone, and visceral recurrence is better identified with PSMA PET/CT. Promising data for novel PSMA radiotracers have been reported.

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