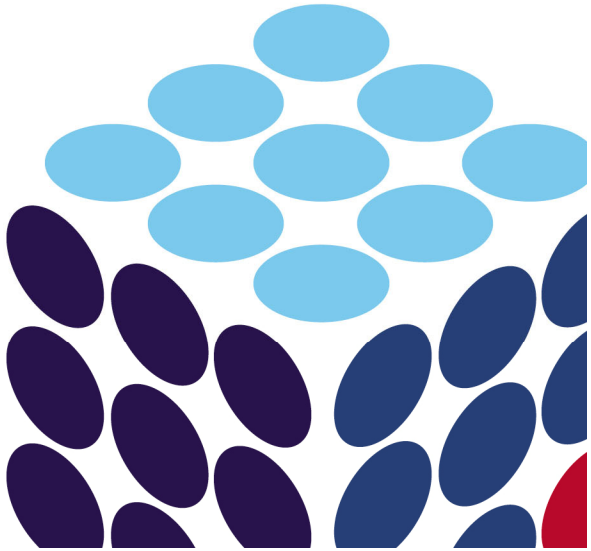
Axumin® Image Interpretation Training
June 2019 v2.0



Disclosures

- David M Schuster, MD provides the narration to the demonstration Axumin® case reviews in this training. Dr Schuster receives research funding from Blue Earth Diagnostics Ltd.
- Blue Earth Diagnostics Ltd provides fluciclovine cassettes to Emory University for research

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Outline of Training

Overview

Axumin® Indication

Axumin (fluciclovine F 18) injection is indicated for positron emission tomography (PET) imaging in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen (PSA) levels following prior treatment

Axumin® (fluciclovine F 18) Injection; US Prescribing Information; Blue Earth Diagnostics, Ltd.

Important Safety Information

- Image interpretation errors can occur with Axumin® PET imaging. A negative image does not rule out recurrent prostate cancer and a positive image does not confirm its presence. The performance of Axumin seems to be affected by PSA levels. Axumin uptake may occur with other cancers and benign prostatic hypertrophy in primary prostate cancer. Clinical correlation, which may include histopathological evaluation, is recommended.
- Hypersensitivity reactions, including anaphylaxis, may occur in patients who receive Axumin. Emergency resuscitation equipment and personnel should be immediately available.
- Axumin use contributes to a patient's overall long-term cumulative radiation exposure, which is associated with an increased risk of cancer. Safe handling practices should be used to minimize radiation exposure to the patient and health care providers.
- Adverse reactions were reported in ≤1% of subjects during clinical studies with Axumin. The most common adverse reactions were injection site pain, injection site erythema and dysgeusia.
- To report suspected adverse reactions to Axumin, call 1-855-AXUMIN1 (1-855-298-6461) or contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
- Full Axumin prescribing information is available at: www.axumin.com.

Important Imaging Considerations

- Axumin® training is provided to you as a background resource to help familiarize you with techniques for the safe and effective usage of Axumin.
- Images should only be interpreted by readers trained in the interpretation of PET images with Axumin.
- The responsibility for the accurate and timely acquisition and interpretation of images using Axumin PET scanning rests with the nuclear medicine physician or radiologist supervising the PET imaging facility.
- Axumin training is not intended to substitute for the independent medical judgment of the physician(s) responsible for the individual patient's management, nor is it a guarantee of any specific clinical results.

Background

Oncologic Imaging with Amino Acids

- Amino acids are in demand for both anabolism & catabolism and are key nutrients for tumor growth
- Involved in signaling via mTOR
- Metabolic shift: glutamine used as an alternative energy source to glucose
- Targeting transport of glutamine inhibits prostate cancer growth in vitro and in PC-3 xenografts

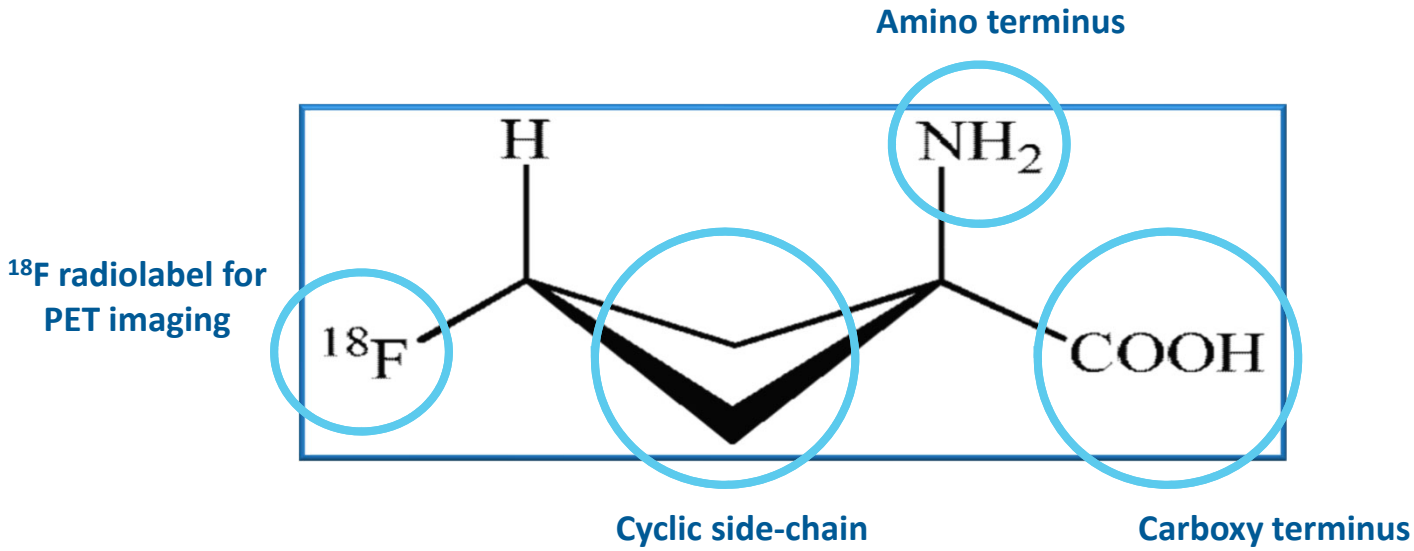
1. Wang et al. J Pathol. 2015;236:278-289.
2. Ganapathy et al. Pharmacology & Therapeutics 2009;121:29.

Axumin® (Fluciclovine F 18)

- Fluciclovine F 18 is an synthetic amino acid PET imaging agent labelled with ^{18}F
  - Transported most like glutamine
- Recognized and taken up by amino acid transporters that are upregulated in many cancer cells, including prostate cancer
- Principle transporters involved in fluciclovine F 18 uptake are LAT1 and ASCT2
  - LAT1 and ASCT2 expression levels have been correlated with a more aggressive phenotype of prostate cancer
- Fluciclovine F 18 is not metabolised or incorporated into newly synthesized proteins

1. Axumin® (fluciclovine F 18) Injection; US Prescribing Information; Blue Earth Diagnostics, Ltd.
2. Oka et al. Nucl Med Biol 2012;39:109–119. 3. Fuchs and Bode. Semin Cancer Biol. 2005;15(4):254-66.

Axumin® (Fluciclovine F 18)



Anti 1-amino-3-18F-fluorocyclobutane-1-carboxylic acid, also known as FACBC) is an artificial amino acid PET imaging agent labelled with ^{18}F (molecular weight 132 g/mole)

Axumin® (fluciclovine F 18) Injection; US Prescribing Information; Blue Earth Diagnostics, Ltd.

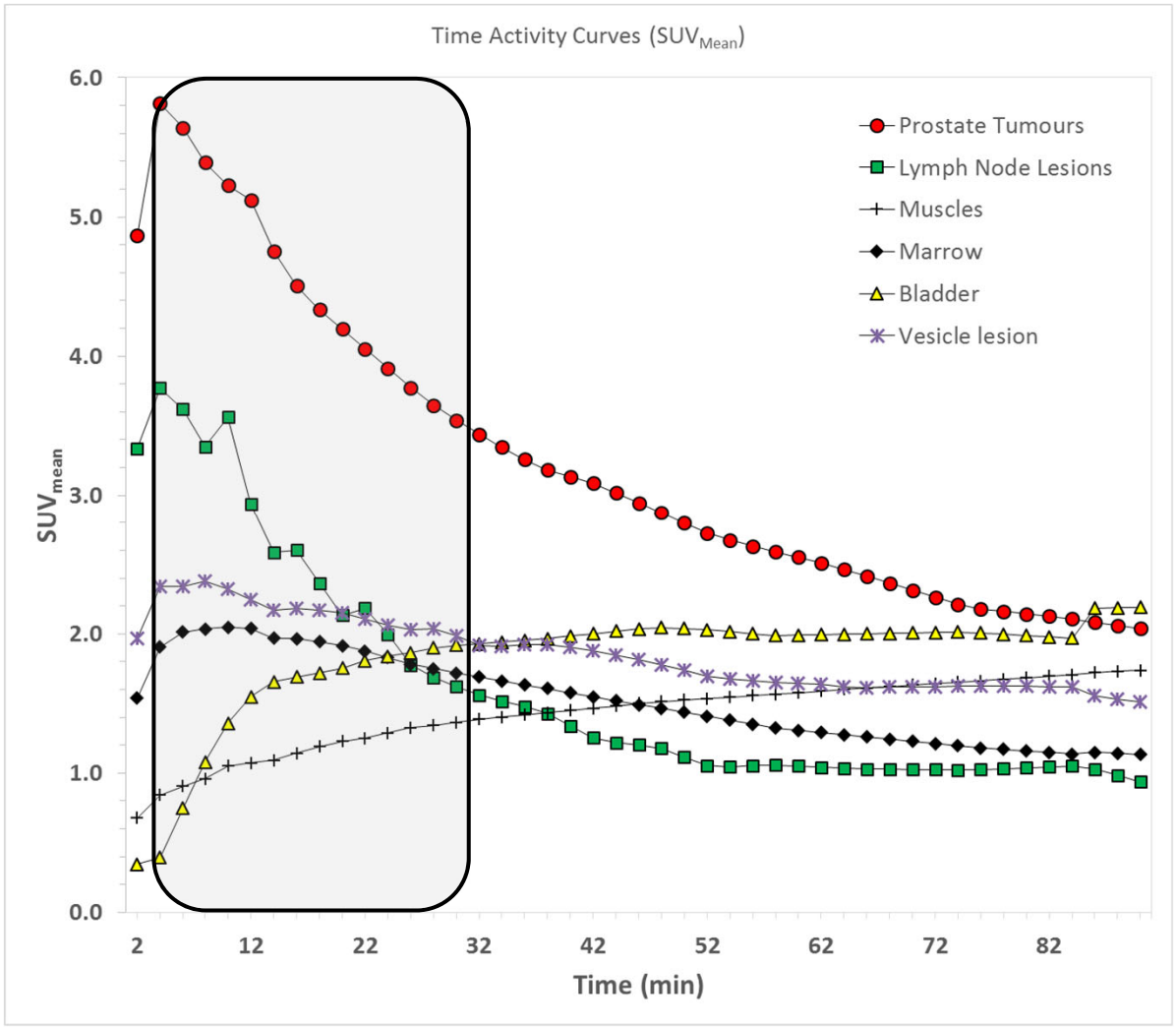
Bio-Distribution: Pharmacokinetics

- Amino acid (AA) transporters ubiquitous throughout body; upregulated in prostate cancer
- Distribution after IV dosing:
  - Liver: 14%*
  - Red bone marrow: 12%*
  - Lung: 7%*
  - Myocardium: 4%*
  - Pancreas: 3%*
  - Over time, Axumin® distributes to skeletal muscle
- Excretion after IV dosing:
  - 3%* excreted in urine (4 hours p.i.)
  - 5%* excreted in urine (24 hours p.i.)
- Typically, minimal to no bladder interference with image interpretation

* % of administered radioactivity

Axumin® (fluciclovine F 18) Injection; US Prescribing Information; Blue Earth Diagnostics, Ltd.

Bio-Distribution: Pharmacodynamics



- Tumor-to-normal tissue contrast is highest between 4 and 10 minutes p.i., with a 61% reduction in mean tumor uptake at 90 minutes
- No extended uptake period
- Fluciclovine F 18 administered on scan table
- Begin PET scanning 3-5 minutes after injection

Note: Grey box denotes typical scan duration; mean and interpolated data from 6 subjects; study GE148-001

1. Axumin® (fluciclovine F 18) Injection; US Prescribing Information; Blue Earth Diagnostics, Ltd.
2. Owenius et al, Internal Blue Earth Diagnostics Ltd. (Dec 2010) Report.

Instrumentation

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PET/CT

- Provided that Axumin® image acquisition guidance is followed, diagnostic performance comparable to that demonstrated at Emory University can be achieved [Section 14, Axumin® (fluciclovine F 18) injection; US prescribing information; Blue Earth Diagnostics, Ltd.]

PET/MRI

- Some institutions are gaining initial clinical experience of imaging Axumin on a PET/MRI scanner and at least one clinical study has been performed
- Contact Blue Earth Diagnostics Medical Affairs with any questions regarding the use of Axumin with PET/MRI imaging

Not recommended for use with Axumin:
Dual-head coincidence cameras or PET stand-alone cameras

1. Axumin® (fluciclovine F 18) Injection; US Prescribing Information; Blue Earth Diagnostics, Ltd.
2. Elschot M et al. J Nucl Med 2018; 59:1913 (ClinicalTrials.gov identifier NCT02562131).

Patient Preparation

- Advise patient to avoid any significant exercise for at least one day prior to PET imaging.
  - If patient has not avoided exercise, biodistribution may be altered and this should be taken into account during image interpretation.
- Advise patients not to eat or drink for at least 4 hours (other than small amounts of water for taking medications) prior to administration of fluciclovine F 18.
  - If patient has not fasted, biodistribution may be altered and this should be taken into account during image interpretation.
- Patients should be encouraged to void approximately **30-60 minutes** before scanning to reduce potential impact of early urinary excretion (in minority of patients) into bladder.
  - If patient voids within 30 minutes prior to start of scan, there is possibility of early appearance of bladder activity and this should be taken into account during image interpretation. This activity is usually generalised, but occasionally may be focal in nature (simulating appearance of a nodule adjacent to the bladder wall), at least on the early images.

1. Axumin® (fluciclovine F 18) Injection; US Prescribing Information; Blue Earth Diagnostics, Ltd.
2. Axumin® (fluciclovine F 18) Imaging & Interpretation Manual (Prostate Cancer) v2.0.

Dosage and Administration

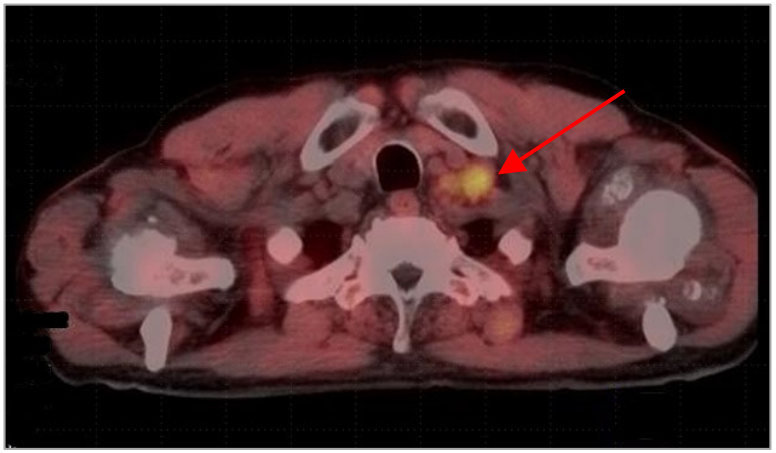
Dosage & Administration

- Administer dose as an intravenous bolus injection while patient is positioned in PET/CT scanner, with their arms adjacent to the torso
- Recommended dose is **370 MBq** (10 mCi)
  - Adult effective dose resulting from administration of recommended activity of 370 MBq of fluciclovine F 18 is 8.2 mSv
  - For administered activity of 370 MBq, typical radiation doses to critical organs, pancreas, cardiac wall and uterine wall are 37.8 mGy, 19.1 mGy and 16.5 mGy, respectively
- Dosimetry comparable to other common PET radiopharmaceuticals

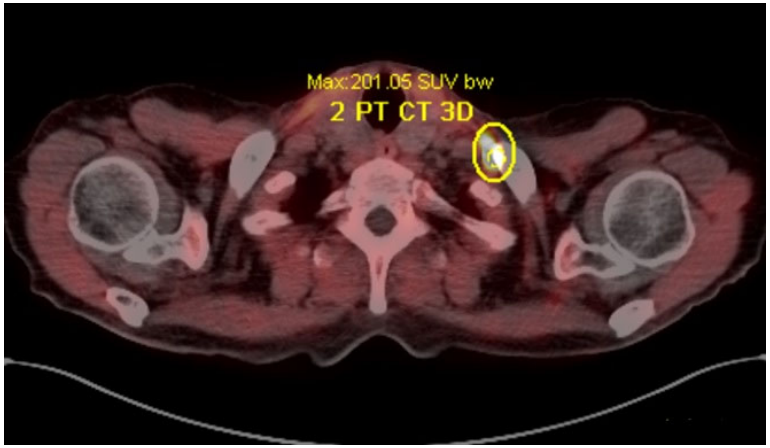
Axumin® (fluciclovine F 18) Injection; US Prescribing Information; Blue Earth Diagnostics, Ltd.

Dosage & Administration

- Injection into right arm is preferred
  - Stasis in left axillary vein may be misinterpreted as metastatic lymph node (Virchow's node)
  - If right arm cannot be used, beware of possibility of image interpretation error



Virchow's node



Stasis (or venous trapping) in axillary vein (SUV_{max} = 201)

1. Oslo University Hospital, Oslo, Norway.
2. Axumin® (fluciclovine F 18) Imaging & Interpretation Manual (Prostate Cancer) v2.0.

Dosage & Administration

- Do not administer a volume of undiluted fluciclovine F 18 that is greater than 5mL
  - This volume keeps administration of all species and solvents within limits generally recognized as safe
- Fluciclovine F 18 dose may be diluted with sterile sodium chloride injection, 0.9%
- After fluciclovine F 18 injection, administer an intravenous flush of sterile sodium chloride injection, 0.9% to ensure full delivery of dose

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Image Acquisition and Reconstruction

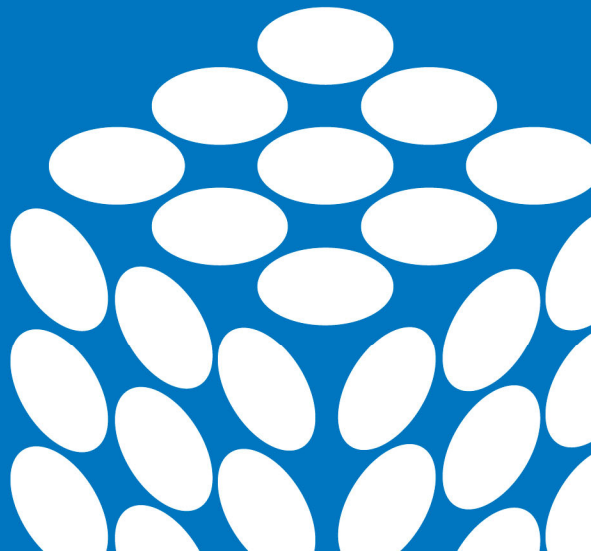


Image Acquisition

- Position the patient supine with arms above head
  - If patient cannot tolerate this position for duration of the study, an alternate position for patient's arms may be used
- CT should be acquired per site standards, however a small lesion seen on PET may be better characterized with a high-quality CT
  - A high quality CT acquisition for anatomic correlation and attenuation correction is recommended
  - Regardless of the CT technique used, a careful review of the CT image is necessary
- Begin PET scanning **3 to 5 minutes** after completion of the fluciclovine F 18 injection
  - If scanning started early, bio-distribution may be altered (e.g. increased blood pool) and this should be taken into account during image interpretation
  - If scanning started late, bio-distribution may be altered (e.g. increased muscle uptake) and this should be taken into account during image interpretation
- Administration of intravenous (iodinated) or oral CT contrast media is not required when acquiring a fluciclovine F 18 PET/CT scan
  - If use of intravenous (iodinated) CT contrast is standard of practice at a site, it is recommended that contrast is administered after completion of fluciclovine F 18 PET/CT scan

1. Axumin® (fluciclovine F 18) Injection; US Prescribing Information; Blue Earth Diagnostics, Ltd.
2. Axumin® (fluciclovine F 18) Imaging & Interpretation Manual (Prostate Cancer) v2.0.

Dosage, Administration & Acquisition

0 minutes

Fluciclovine (^{18}F) administration (arms down)

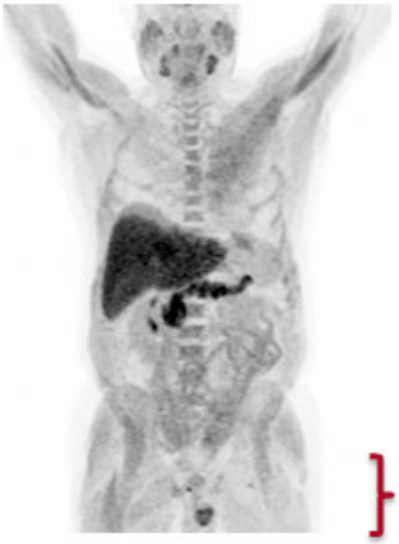
1 minute

Move arms above head

1 minute 30 seconds
(approximate)

CT for attenuation correction and anatomic correlation

4 minutes ± 1 minute
(PET acquisition start time)



Static PET acquisition Mid-thigh (just below the pelvis) to base of skull

It is **very important** that prostate bed is centrally positioned within first bed position and that inguinal lymph nodes are included

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2. Axumin® (fluciclovine F 18) Imaging & Interpretation Manual (Prostate Cancer) v2.0.

Image Acquisition

- Recommended that image acquisition should start at mid-thighs, just below the pelvis
  - It is **very important** that prostate bed is centrally positioned within first bed position and, also, that inguinal lymph nodes are included
  - Coverage of imaging should extend to base of skull
- Typical total scan time is between 20 to 30 minutes
  - Actual scan time is typically dependent on scanner type, scan length, and time per bed position/bed speed (scanners with continuous bed motion)
  - Recommended to scan for **5 minutes per bed** position over pelvis (i.e. pubic symphysis to iliac crest) to increase sensitivity of detection of prostate cancer recurrence in sites typical for such recurrence
    - However, acquisition time is scanner specific; start time of scan after injection (3-5 minutes, target 4 minutes) is more important
    - For remaining bed positions (i.e. iliac crest to base of skull) 5 minutes per bed position is recommended, although this may be reduced to 3 minutes per bed position (if PET/CT allows this adjustment and site is experienced with such image acquisition procedures)

Axumin® (fluciclovine F 18) Injection; US Prescribing Information; Blue Earth Diagnostics, Ltd.

Image Reconstruction

- Highest quality scanner at an institution should be used because of potential impact of lesion size on image interpretation
- Reconstruction algorithms should be based on manufacturer's recommendations
  - Reconstruction modifications can best be achieved using the manufacturer's guidelines along with institution's physician and physicist recommendations
- If a scanner has time-of-flight (ToF), an iterative reconstruction algorithm, a Bayesian penalized-likelihood reconstruction algorithm or other new reconstruction algorithm, it is recommended that these features be utilized
  - However, if resolution recovery is utilized, physician should be aware of advantages and disadvantages
  - Resolution recovery may help with detection of small lesions, but size criteria for evaluation may change
    - For example, a 1 cm lymph node without resolution recovery may be equivalent to a 7 or 8 mm lymph node with resolution recovery

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2. Axumin® (fluciclovine F 18) Imaging & Interpretation Manual (Prostate Cancer) v2.0.

Interpretation Criteria

Interpretation Criteria: Read Methodology

- Localization of prostate cancer recurrence in sites typical for prostate cancer recurrence is based on Axumin® uptake in comparison with tissue background
- Imaging interpretation is predominantly qualitative, based on typical sites of recurrence of prostate cancer
- General guidance is to report inside-out (i.e., assess central areas of focal uptake before assessing the periphery)
  - It is critically important for the reader to know typical sites of metastases and recurrence of prostate cancers, as well as the normal distribution of Axumin, normal variants and potential pitfalls
  - When interpreting Axumin scans, the physician should be aware of differences in biodistribution between other commonly used radiopharmaceuticals, particularly [^{18}F]-FDG, and Axumin
- As with any imaging, full correlation with all available information (e.g. medical history, laboratory results, bone scans, CT and MRI scans) should occur and may improve the confidence level of interpretation of the PET scan

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Interpretation Criteria: Read Methodology

- Tissue background is measured in blood pool or bone marrow

Volume of interest for blood pool

Measure a volume that encompasses the lumen of the aorta or largest artery (~1 cm) at or about the level of the lesion **(in same bed position frame)**

Volume of interest for bone marrow

Measure the largest volume that encompasses marrow in normal third lumbar vertebra (L3 or nearest adjacent normal vertebra if uptake in L3 is not physiological)

Interpretation Criteria: Read Methodology

- Thresholds based on lymph node sizes (i.e. < or ≥ 1 cm), referred to throughout the interpretation criteria, are based on the **maximum** dimension of the lymph node for the purpose of visual interpretation
  - Nodal short axis or bi-dimensional measurements should still be reported per the interpreting reader's usual practice
- SUV measurements should be normalized by body weight
- Use of multiple orthogonal planes of view (for example: axial, sagittal, and coronal) is recommended
- Maximum Intensity Projection (MIP) may be useful for the detection of lesions in bone, as well as in lymph nodes
- Use of color tables are a personal preference for the reader, based on the image review workstation and reader's experience

Interpretation Criteria: Read Methodology

- To ensure that all organs are being reviewed appropriately, the following PET window display guidelines are suggested

Prostate

View with a variety of PET and CT windows, start with pancreas and liver fairly intense

Lymph nodes

Window with lower upper-threshold SUV intensity; consider optimizing setting for lesion detectability

Liver

Review liver with similar windowing as brain in [^{18}F]-FDG, upper threshold should be higher than SUVmax in normal liver

Bone

Use the Maximum Intensity Projection (MIP) image

- The most appropriate windowing is typically scanner/workstation dependent and must be selected based on the clinical judgement and experience of the reader

Prostate Bed: Post-Prostatectomy

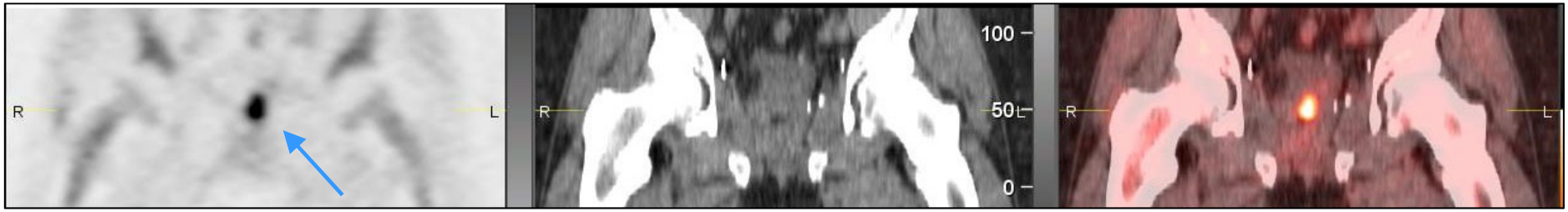
No focal uptake	Likely benign
Focal uptake between blood pool and bone marrow	Follow-up recommended*
Focal uptake equal to or greater than bone marrow	Likely malignant

* Uptake not meeting threshold for malignancy (equivocal) may require follow-up and clinical correlation.

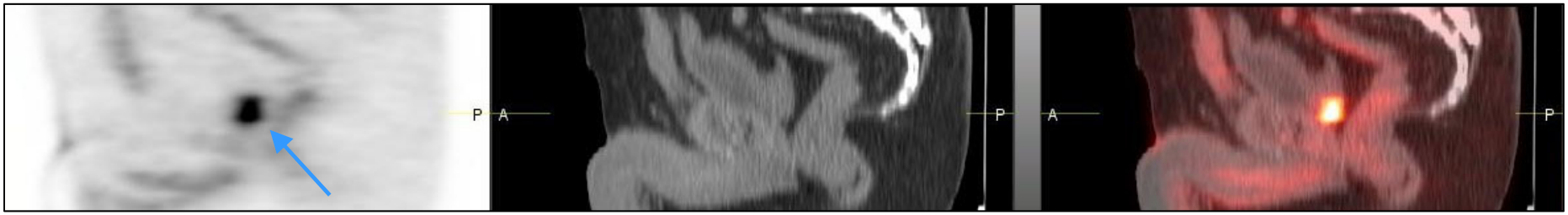
- Uptake on anatomical correlate < 1 cm, significantly greater than blood pool (i.e., close to bone marrow), may also be considered suspicious for malignancy; MRI correlation is suggested
  - If a lesion of this size does not meet this threshold, it should be reported as such but requires follow-up and clinical correlation
- Sagittal images are useful in the evaluation of the anastomotic site

Prostate Bed: Post-Prostatectomy

- Subject presented with elevated PSA of 43.5 ng/ml
- Prostate bed recurrence detected (blue arrow)



Coronal view



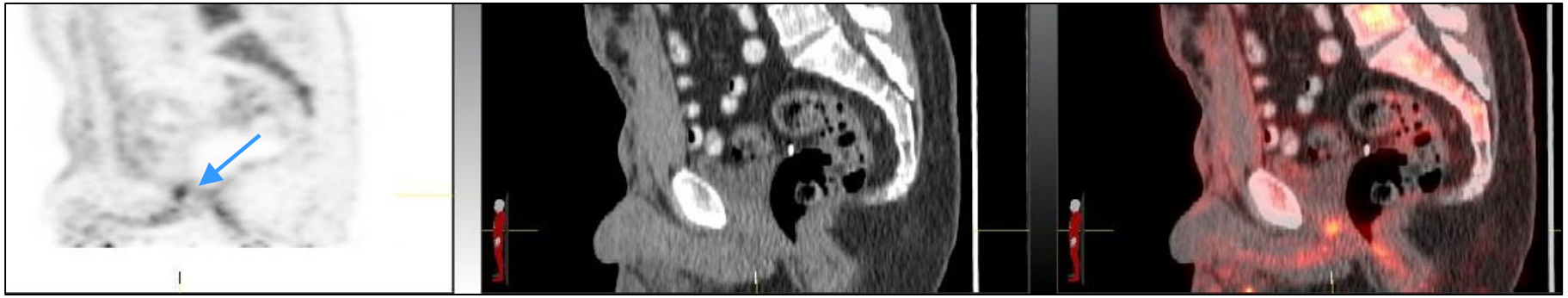
Sagittal view

Emory University, Atlanta, GA, USA.

Prostate Bed: Post-Prostatectomy

- Subject presented with elevated PSA of 0.29 ng/ml
- Recurrent prostate cancer detected in anastomotic area of bladder and urethra (blue arrow)

Coronal view

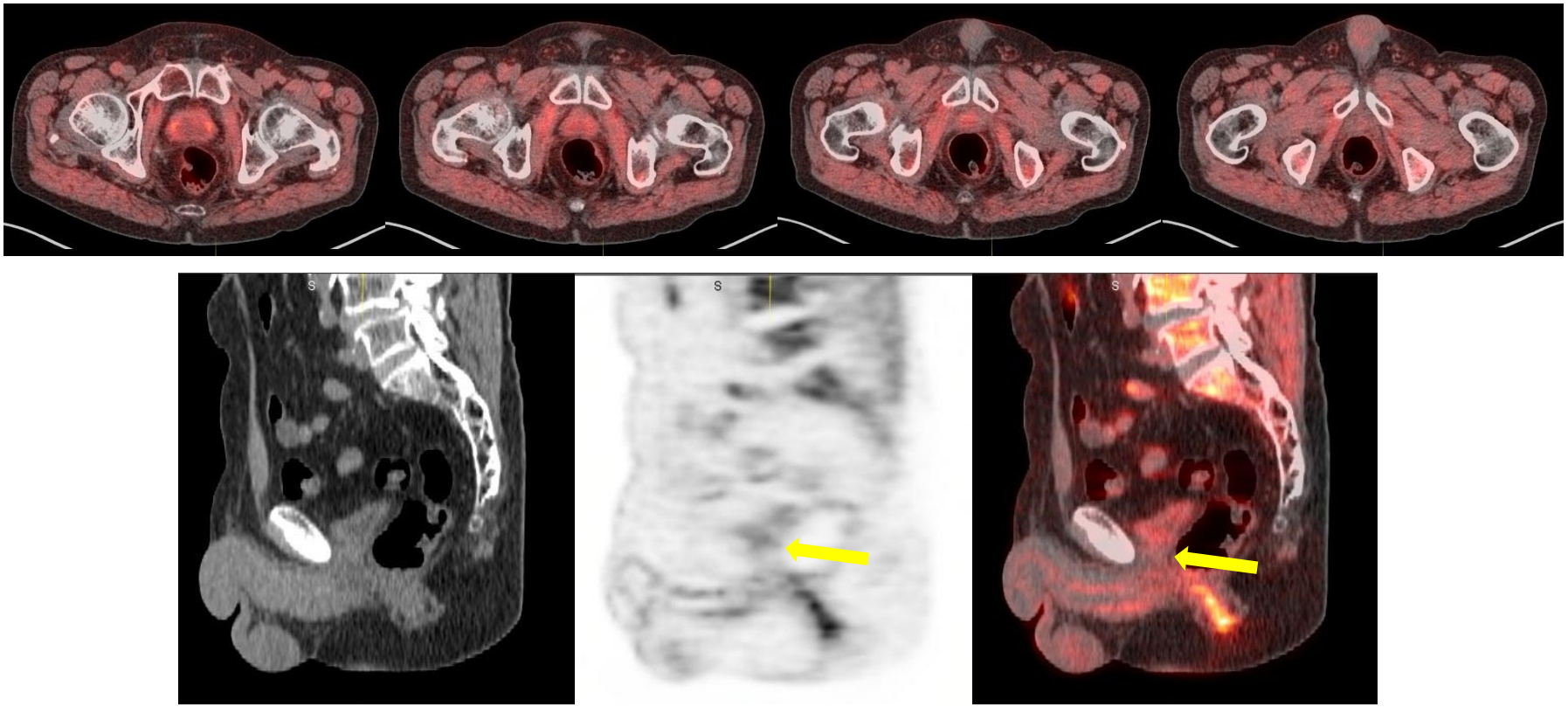


Sagittal view

Emory University, Atlanta, GA, USA.

Prostate Bed: Post-Prostatectomy

- No uptake at anastomotic region on sagittal view (yellow arrow)
- Cranial to caudal review demonstrated mild symmetric uptake in bladder wall
- Image interpretation: negative prostate bed



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Prostate Bed: Non-Prostatectomy (Intact Prostate)/Prior Therapy

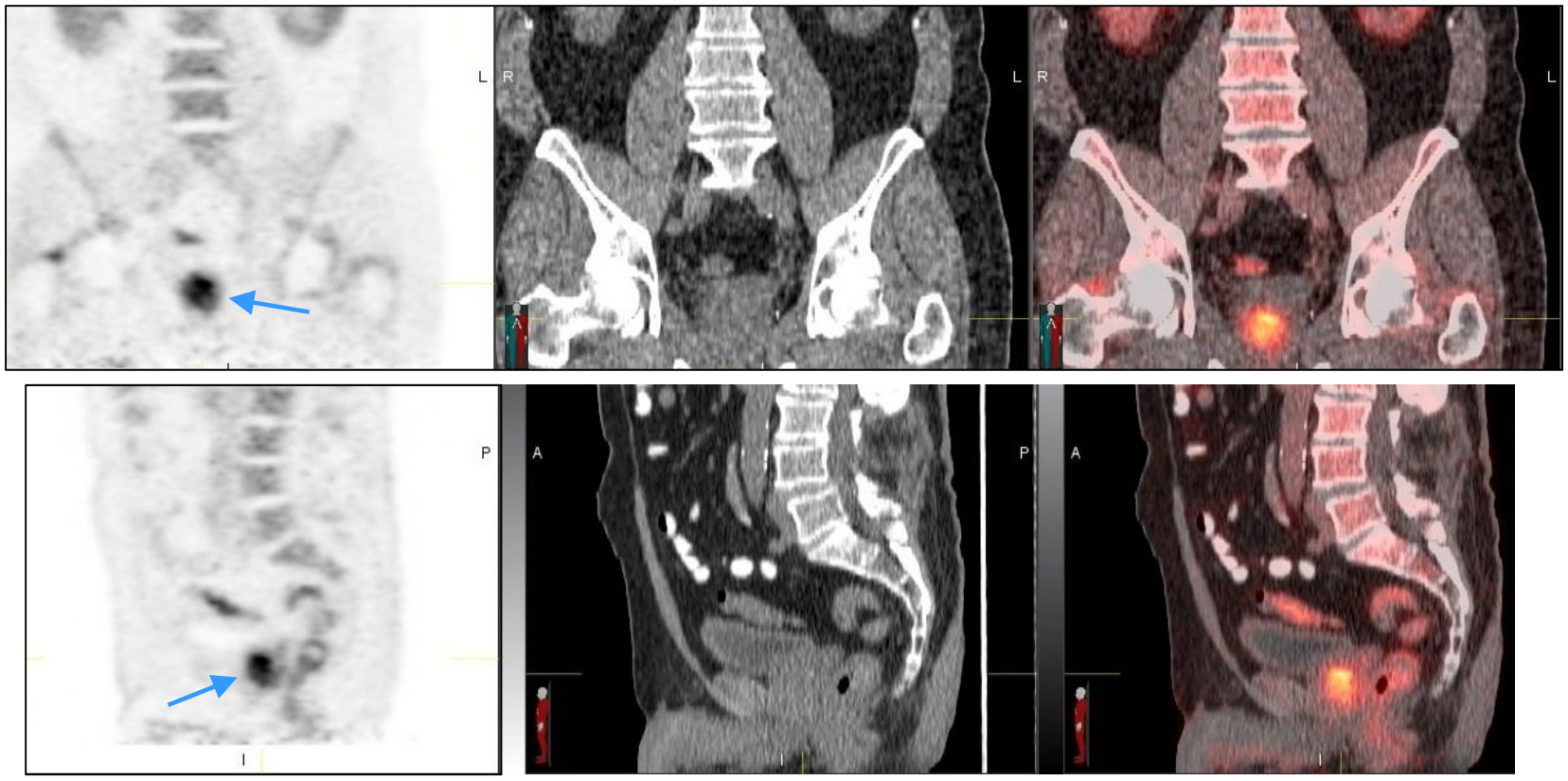
No focal uptake	Likely benign
Diffuse, focal, or multi-focal uptake between blood pool and bone marrow	Follow-up recommended*
Diffuse, focal, or multi-focal uptake equal to or greater than bone marrow	Likely malignant

* Uptake not meeting threshold for malignancy (equivocal) may require follow-up and clinical correlation.

- Uptake on anatomical correlate < 1 cm, significantly greater than blood pool (i.e., close to bone marrow), may also be considered suspicious for malignancy; MRI correlation is suggested
  - If a lesion of this size does not meet this threshold it should be reported as such but requires follow-up and clinical correlation
- Focal uptake with calcification may indicate benign inflammation; MRI correlation is suggested
- Anecdotally, median prostate lobe uptake (central base invaginating into bladder) has a higher false positivity

Prostate Bed: Non-Prostatectomy (Intact Prostate)/Prior Therapy

- Subject presented with rising PSA (10.6 ng/mL; nadir 6.6ng/ml), post-cryotherapy
- Image interpretation: positive prostate (blue arrows); negative extra-prostatic
- PSA decreased to 0.49 ng/ml post-salvage cryotherapy



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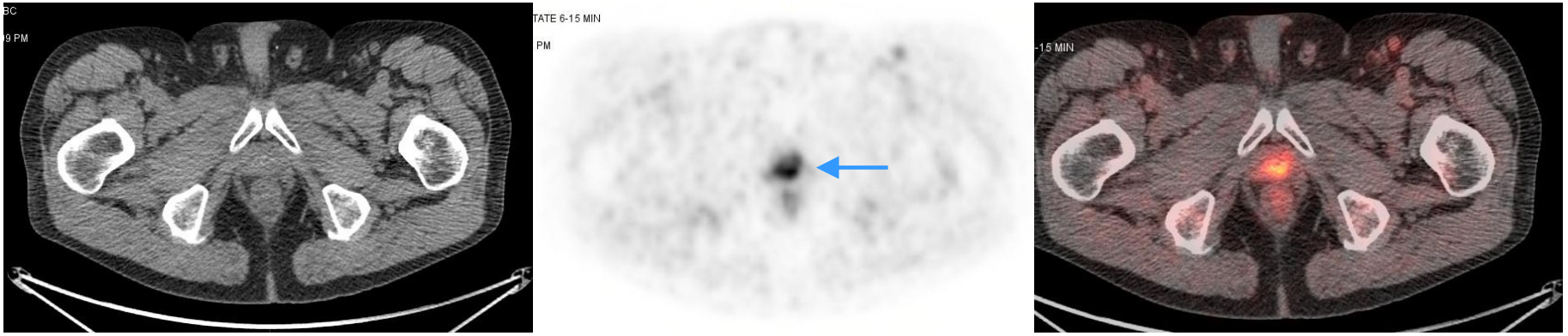
Prostate Bed: Non-Prostatectomy (Intact Prostate)/Prior Therapy

- Image interpretation (top row): positive prostate, biopsy proven malignant



- Image interpretation (bottom row), diffuse homogeneous activity not significantly greater than marrow visually (borderline), biopsy proven benign

Emory University, Atlanta, GA, USA.

Seminal Vesicles

- In seminal vesicles, with or without the prostate present, symmetric bilateral uptake similar to blood pool is likely physiologic
- Asymmetric seminal vesicle uptake between blood pool and marrow may increase the suspicion for malignancy; consider pelvis MRI for further characterization

Lymph Nodes

Lymph nodes in a typical site of recurrence of prostate cancer, equal to or greater than 1 cm (maximum dimension)

Uptake less than or equal to blood pool	Likely benign
Uptake between blood pool and bone marrow	Follow-up recommended*
Uptake equal to or greater than bone marrow	Likely malignant

* Uptake not meeting threshold for malignancy (equivocal) may require follow-up and clinical correlation.

- Uptake in lymph nodes ≥ 1 cm in a typical site of recurrence of prostate cancer should have a higher threshold for positivity relative to lymph nodes < 1 cm
  - If a node ≥ 1 cm does not meet this threshold of equal to or greater than bone marrow (including those approaching, but not reaching, bone marrow) it should be reported as such but requires follow-up and clinical correlation

Lymph Nodes

Lymph nodes in a typical site of recurrence of prostate cancer, less than 1 cm (maximum dimension)

Uptake less than blood pool	Likely benign
Uptake greater than or equal to blood pool, but not close to bone marrow	Follow-up recommended*
Uptake significantly greater than blood pool, close to, equal to, or greater than bone marrow	Likely malignant

* Uptake not meeting threshold for malignancy (equivocal) may require follow-up and clinical correlation.

- Uptake in a lymph node < 1 cm in a typical site of recurrence of prostate cancer has a lower threshold for positivity, which is considered significantly greater than blood pool (i.e. close to, equal to, or greater than marrow)
  - If a node < 1 cm does not meet this threshold it should be reported as such but requires follow-up and clinical correlation

Lymph Nodes: General Guidance

The following factors should be considered in evaluation of lymph nodes, especially for lymph nodes not meeting threshold for malignancy:

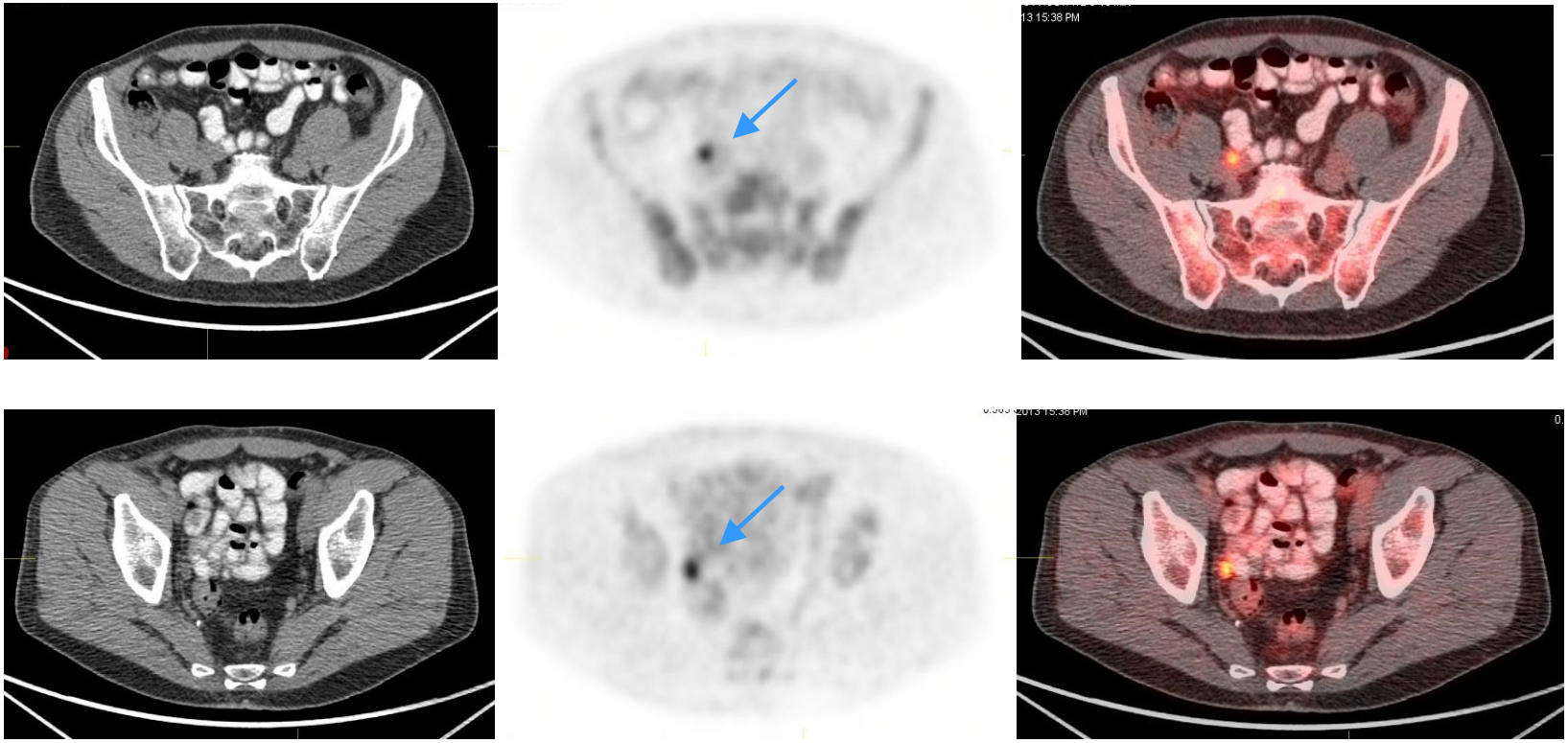
Location:

- For atypical sites of recurrence (e.g., inguinal, hilar, and axillary nodes) mild symmetric uptake is considered physiologic uptake. However, if the node is present within the context of other recurrent disease, particularly pelvic metastases, it may also be considered suspicious.
- Distal external iliac nodes may also be suspicious in isolation. Mild symmetric uptake may be considered physiologic uptake. However, if the node is asymmetric or present within the context of other recurrent disease, it may also be considered suspicious.
- Note that the presence of nearby vascular grafts, orthopaedic hardware or recent invasive procedures could cause false positive uptake in these nodal groups.

- **Shape:** Round nodes are more suspicious than curvilinear nodes on CT.
- **Grouping:** Depending on category, a group of nodes in a typical location is more suspicious than a solitary node, and in that case a single node with higher uptake than surrounding lymph nodes may still be suspicious even if not meeting the threshold for malignancy.
- **Necrosis:** A metastatic necrotic node may not have increased Axumin® uptake.

Lymph Nodes

- Subject presented with rising PSA (2.31 ng/mL), post-radiotherapy and brachytherapy
- MR negative for extra-prostatic disease
- Image interpretation: positive sub-cm right common iliac and obturator nodes (blue arrows), histopathological sampling confirmed malignancy



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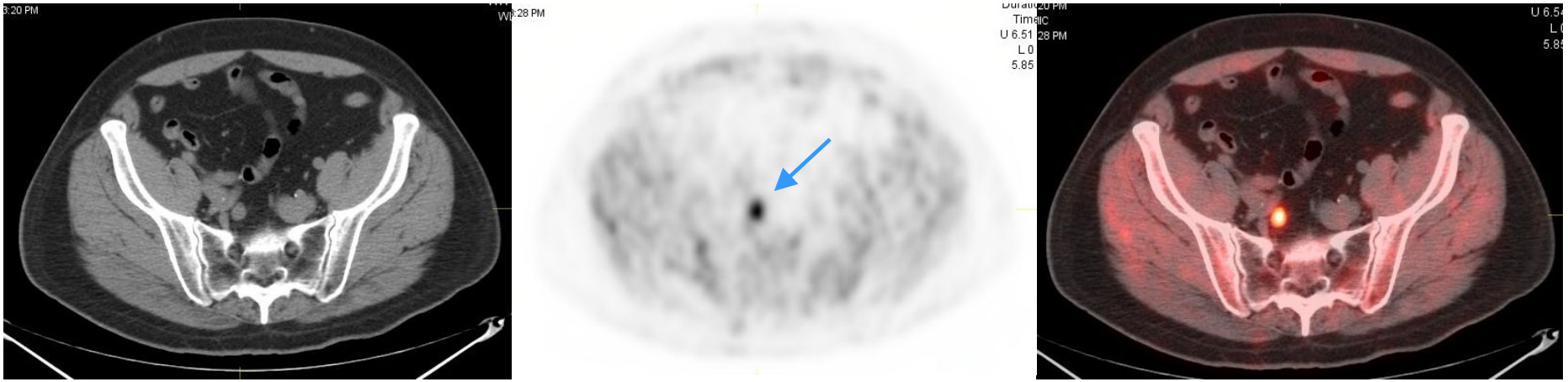
Lymph Node

- Additional images from the subject with rising PSA (2.31 ng/mL), post-radiotherapy and brachytherapy



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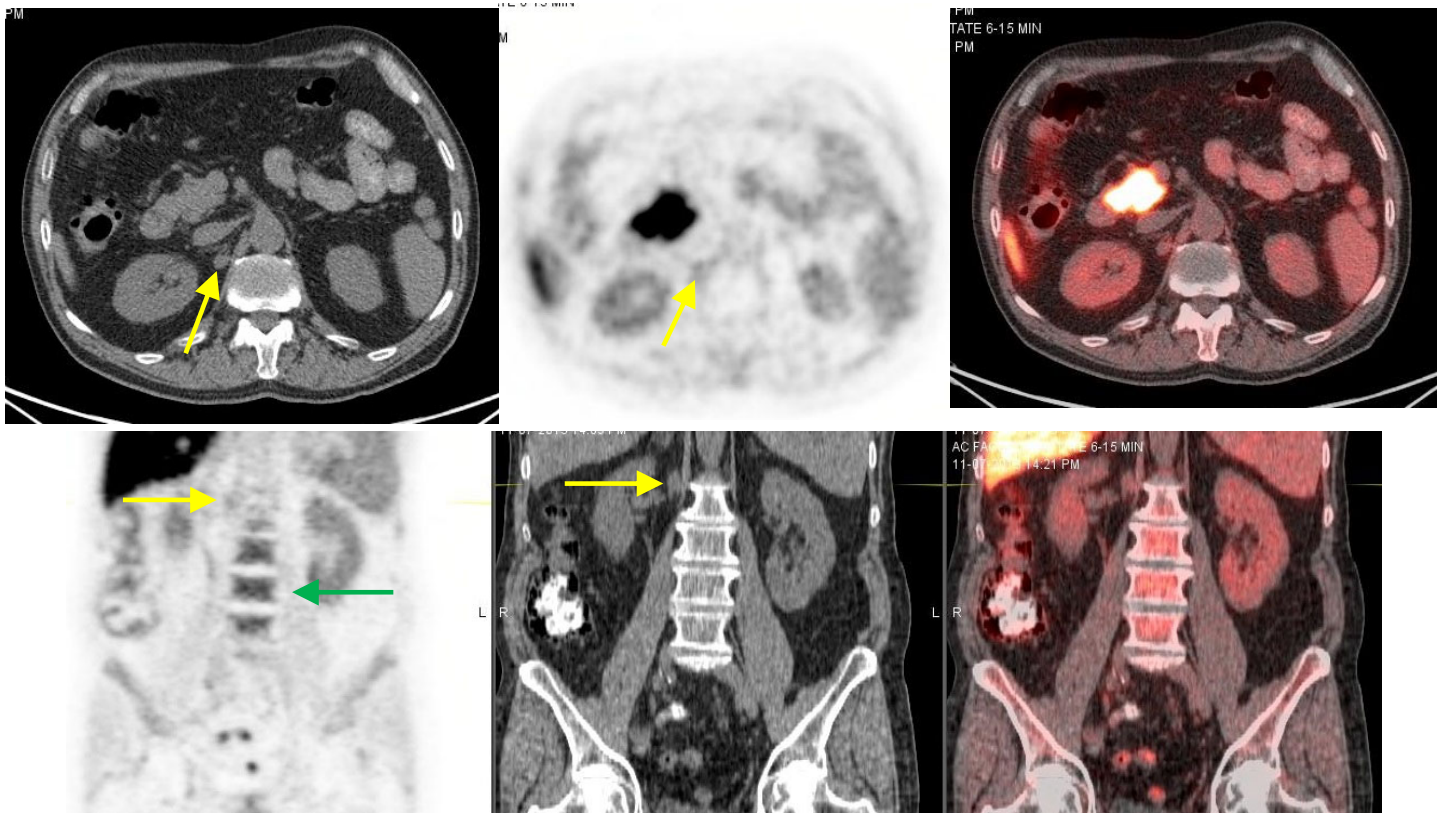
Lymph Nodes

- Patient presented with rising PSA post-therapy
- 1 cm node identified (yellow arrows) with uptake not ≥ marrow (green arrow)
- Image interpretation: negative, biopsy confirmed benign



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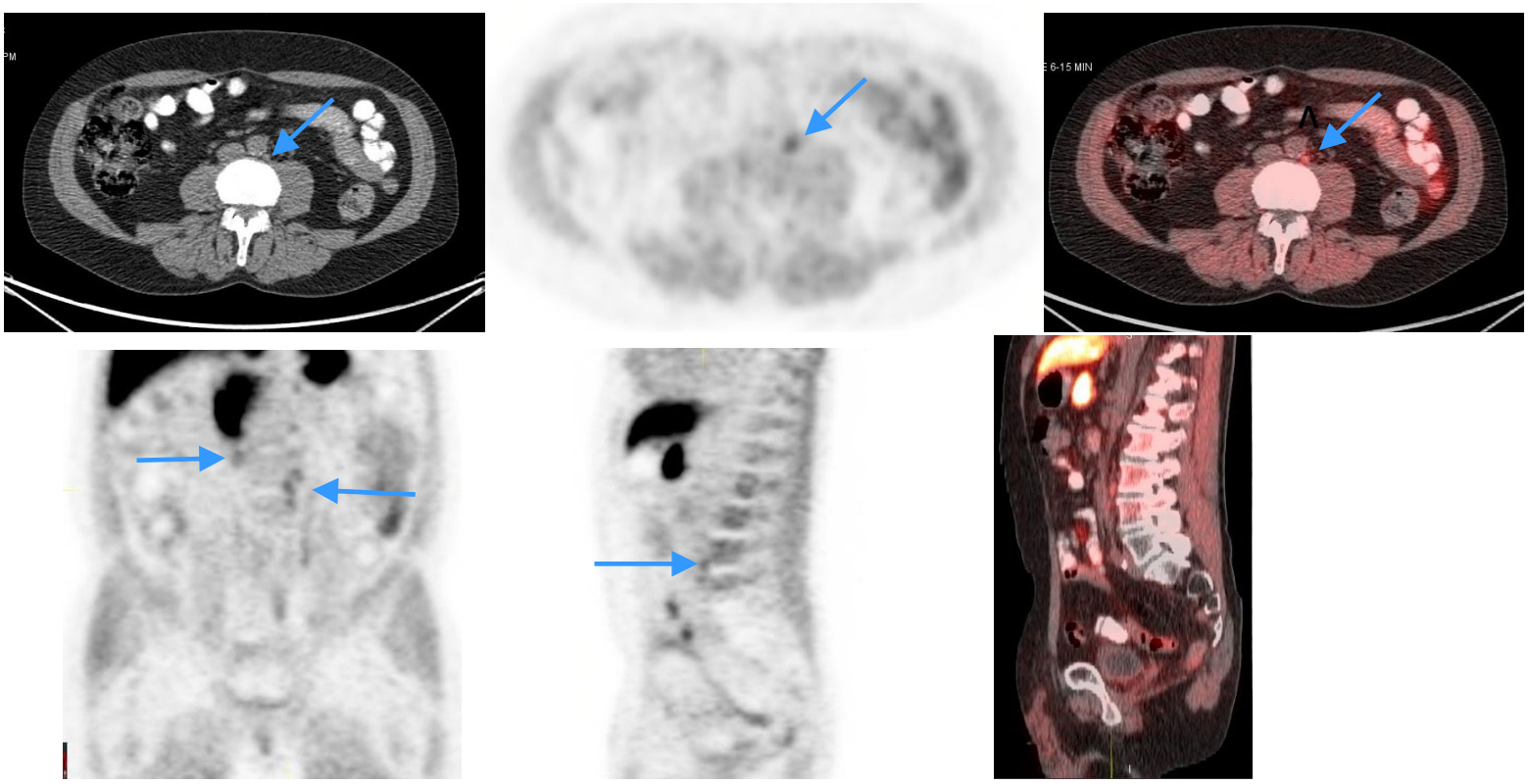
Lymph Nodes

- 3-5 mm retroperitoneal nodes (blue arrows), significantly greater than blood pool visually.
- Image interpretation: suspicious for prostate cancer (especially considering nodes in suspicious groupings). Compare to sagittal midline spine; since appear similar to marrow even at this size, consider malignant. Quantitation added confidence.



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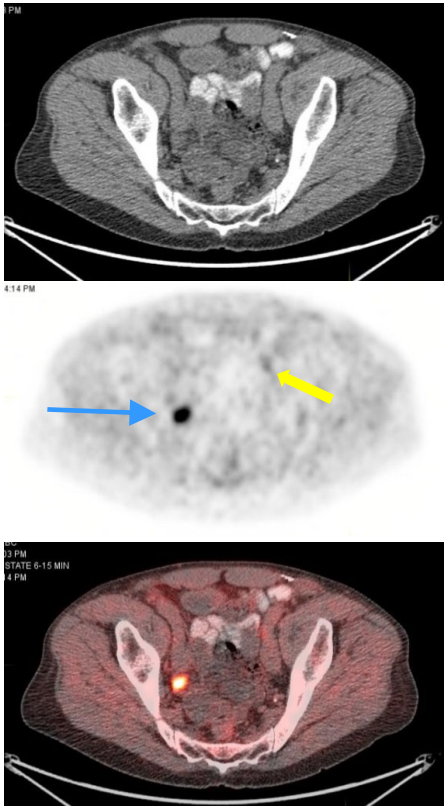
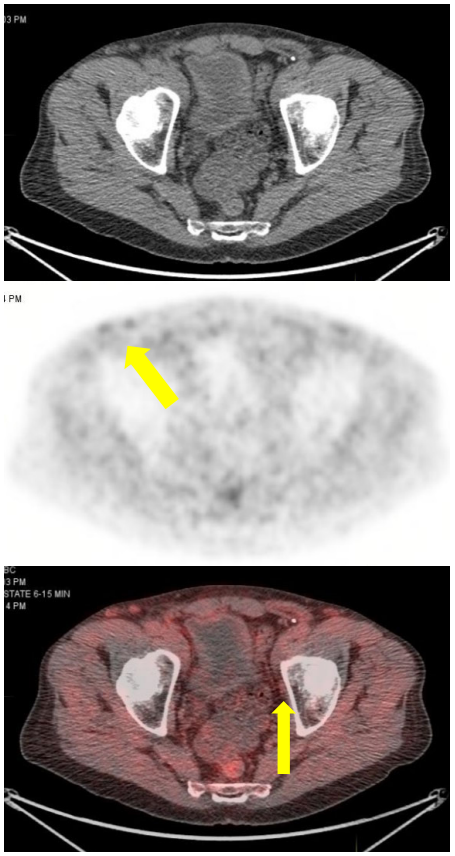
Lymph Nodes

- 1.5 x 1.2 cm right iliac bifurcation node, is suspicious for a metastasis (blue).
- Mild uptake in left ext iliac, left obturator, or symmetric inguinal nodes (yellow) is likely benign
- Nodal dissection was malignant only where fluciclovine F 18 was hotter than marrow





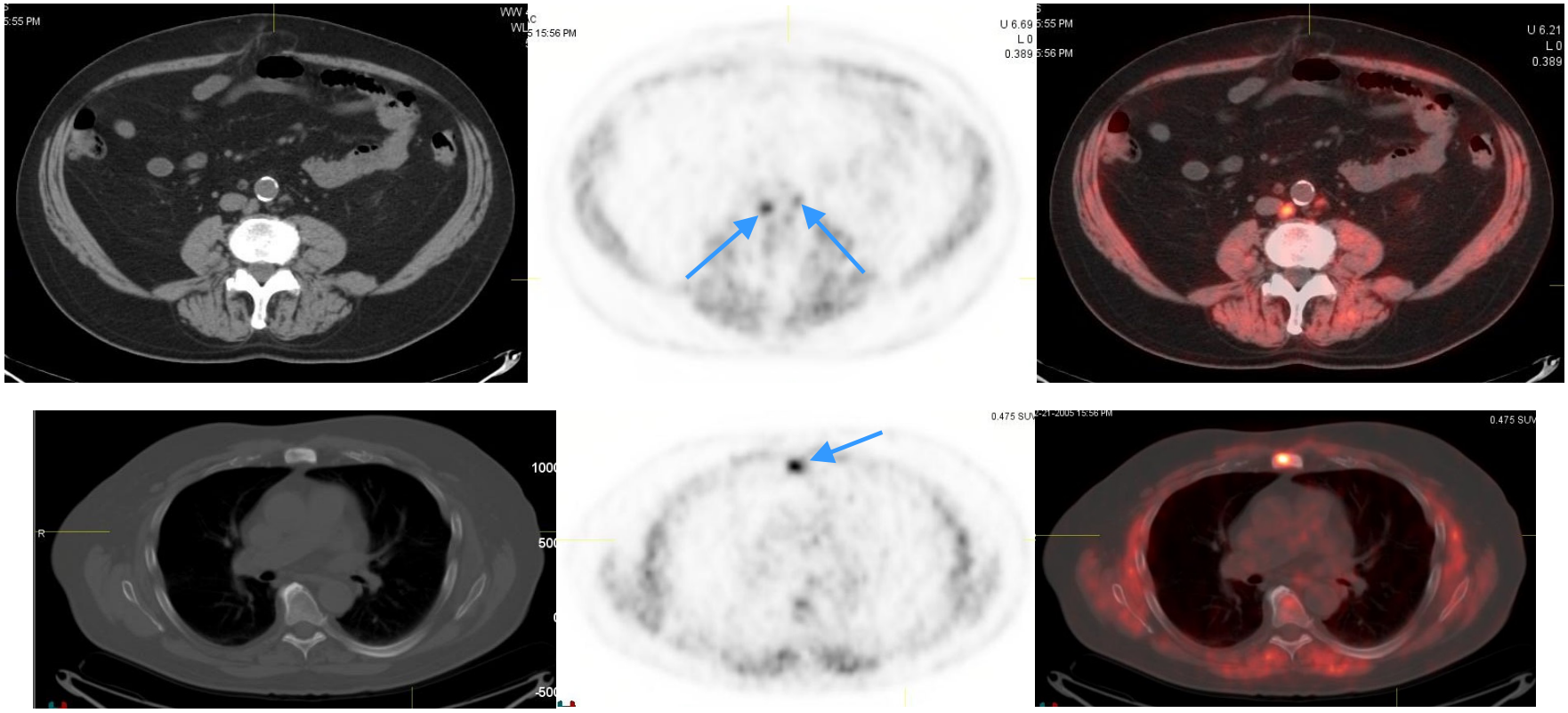
Emory University, Atlanta, GA, USA.

Bone

- Focal uptake clearly visualised on Maximum Intensity Projection (MIP) or PET-only images, can be considered suspicious for cancer
- A bone abnormality visualized on CT (e.g. sclerosis without uptake) may still represent a metastasis. Alternative imaging, for example, MRI, (^{18}F)-NaF PET, ^{99m}Tc SPECT/CT bone scan or standard bone scintigraphy should be considered
- Due to normal physiologic heterogeneity of bone marrow, appropriate PET display windowing must be used
- Increased uptake in bone may be seen in the setting of trauma (including compression fractures) or occasionally degenerative changes
- Skeletal metastases which resemble Schmorl's nodes, but with uptake within them, have been described

Bone

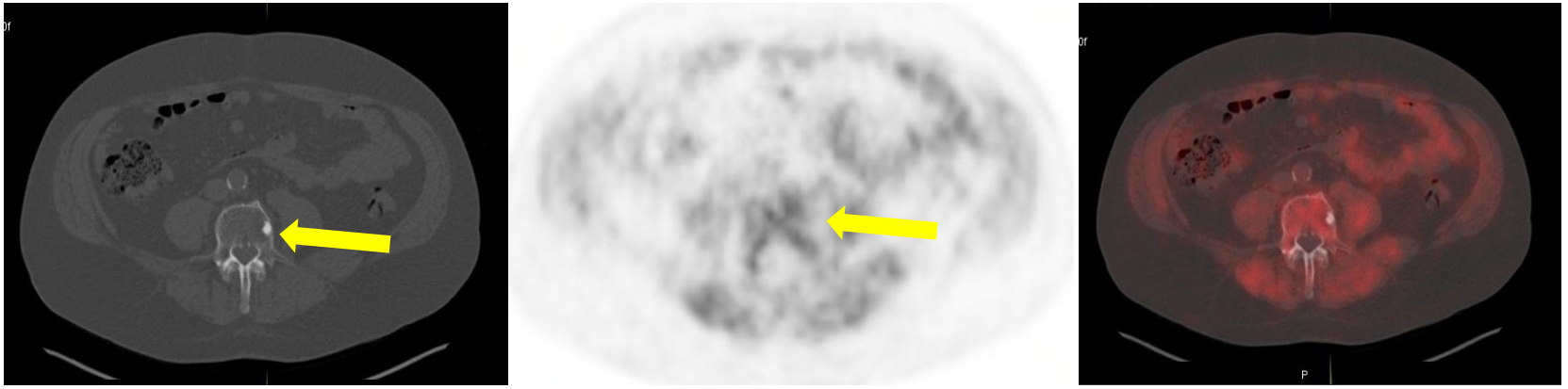
- Patient presented with rising PSA (9.5 ng/mL), post-prostatectomy and salvage radiotherapy.
- Image interpretation: multiple foci positive (including sub-cm retroperitoneal nodes and sternum) (blue arrows). Sternum biopsy positive prostate cancer.



Emory University, Atlanta, GA, USA.

Bone

- Dense sclerotic lesion, without uptake; cannot exclude metastases (yellow arrow). Recommend follow-up imaging such as MR or bone scan.



- Mildly sclerotic lesion, without fluciclovine F 18 (yellow arrow); would expect greater fluciclovine F 18 uptake so considered negative despite positive MR. Biopsy negative.

Emory University, Atlanta, GA, USA.

Liver

- Due to normal physiologic activity in the liver, metastases may be obscured, and appropriate PET display windowing must be used (upper window level > normal liver)
- Uptake in liver greater than normal liver tissue is considered suspicious for malignancy
- Lesions seen on CT or MRI with uptake less than normal liver (but higher than bone marrow) may represent malignant processes
    - Can be further evaluated with anatomical imaging such as multi-phase liver MRI or CT

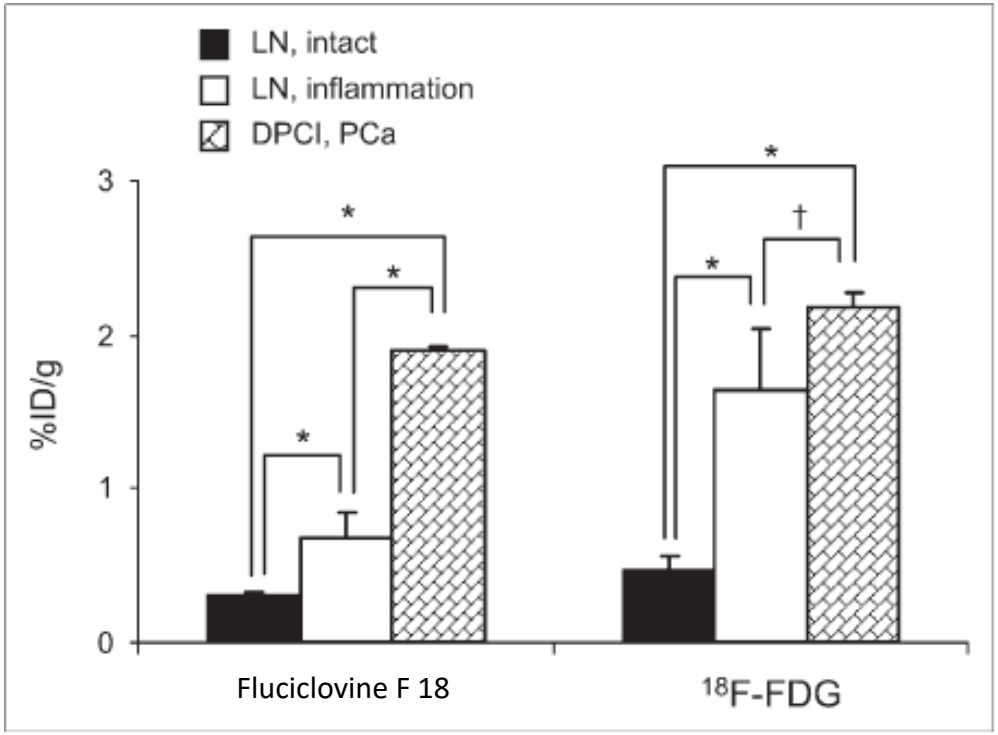
Bladder

- Mild (similar to blood pool) symmetric bladder wall activity is typically benign
- Asymmetric significant uptake may represent malignancy and should be further evaluated
- Accumulation of Axumin® may simulate the appearance of a nodule adjacent to the bladder wall, particularly in the dependent portion of the bladder

Inflammation

Inflammation

- Research has been undertaken in a series of in-vitro and small animal models
- Amino acid imaging is believed to be less prone to false positive inflammatory uptake
- However, amino acid transporters are also overexpressed in benign inflammation
- Graph (right) demonstrates the uptake of fluciclovine F 18 in normal popliteal lymph node (LN, intact), popliteal lymphadenitis (LN, inflammation), and subcutaneous prostate cancer in DPCI (rat) model



*P < 0.01; Each bar represents mean ± SD

1. Oka et al. J Nucl Med 2007 Jan;48:46. 2. Oka, et al. Mol Imaging Biol 2014;16:322.
3. Kanagawa, et al. Nucl Med Biol 2014;41:545.

Incidental Uptake and Variants

Incidental Uptake and Variants

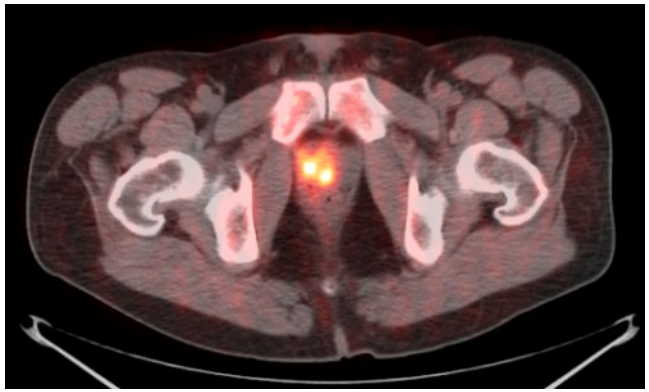
- In order to interpret images, the physician should be aware of potential for fluciclovine F 18 uptake in areas of benign pathology and other incidental cancers.
- The following slides:
  - Describe physiological variants and incidental findings noted following use of fluciclovine F 18 in patients with various conditions
  - Provide examples resulting from non specific uptake of this amino acid tracer in areas of inflammation and in other benign and malignant pathologies
  - Represent potential incidental findings with fluciclovine F 18 outside of its indicated use for positron emission tomography (PET) imaging in men with suspected prostate cancer recurrence

False Positives

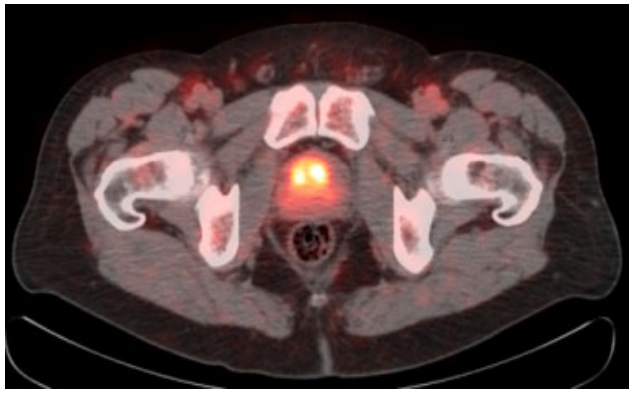
- Axumin® uptake is not specific for prostate cancer and may occur with other types of cancer, prostatitis and benign prostatic hyperplasia.
- False-positive cases have also been described in association with an inflammatory response after cryotherapy and radiation artefacts in patients previously treated with radiotherapy.
- Clinical correlation, which may include histopathological evaluation of the suspected recurrence site, should be considered where appropriate.
- PSA levels seem to have an impact on the detection rate of Axumin.
    - In general, patients with negative scans had lower PSA levels than those with positive scans.
- Physicians should be aware of potential for Axumin uptake in areas of benign pathology and other incidental cancers. These potential incidental findings with Axumin are outside of its indicated use for positron emission tomography (PET) imaging in men with suspected prostate cancer recurrence.

Incidental Uptake and Variants

- Fluciclovine F 18 uptake in areas of benign prostate pathology may be indistinguishable from uptake in areas of prostate cancer



Prostatitis



Benign prostatic hyperplasia

Schuster et al. J Nucl Med 2014;55:1986-92.

Incidental Uptake and Variants

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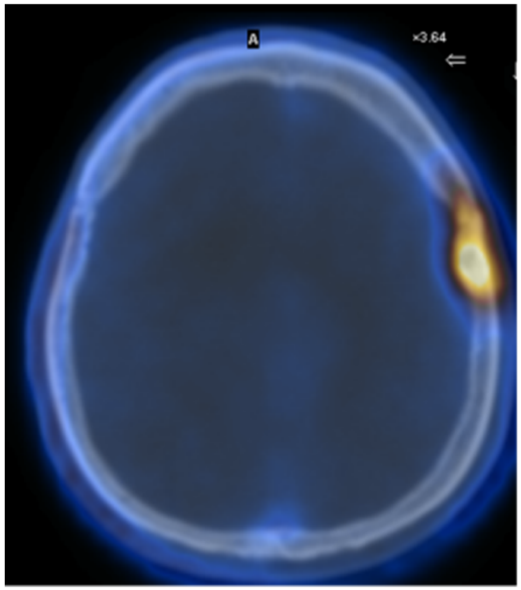
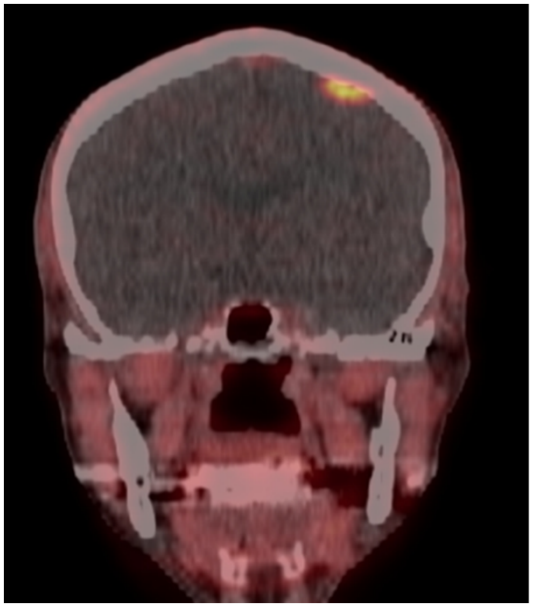
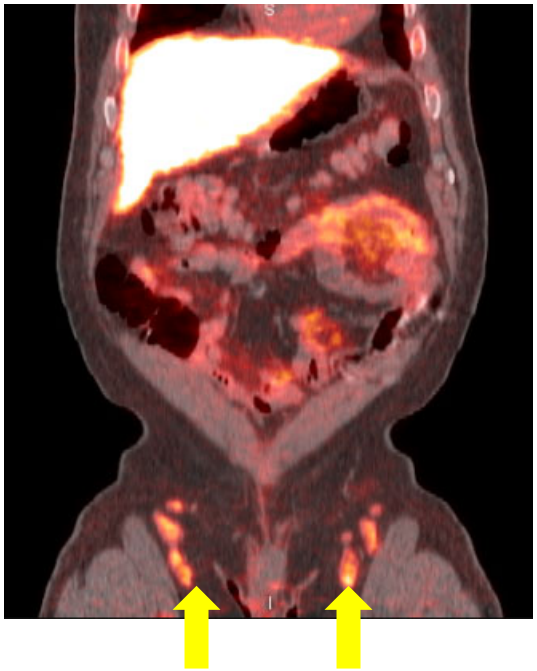
Osteoid osteoma



Meningioma



Ringworm (dermatophytosis)

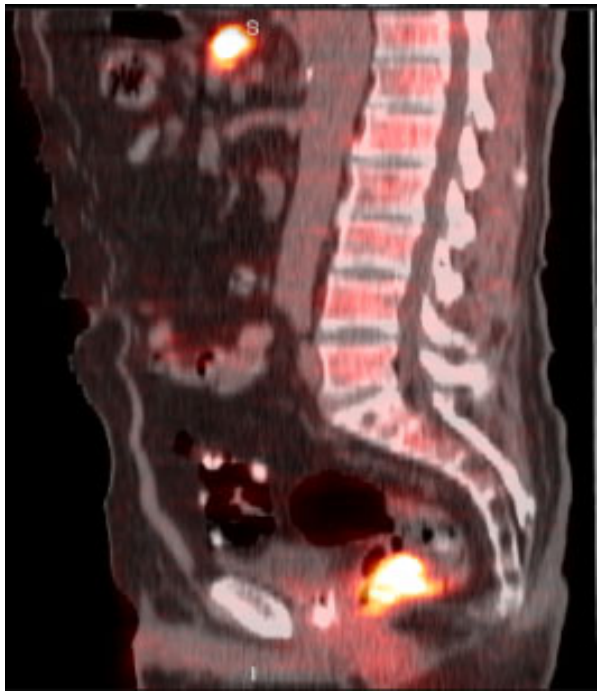


Mild symmetric inguinal nodal uptake is commonly present. It may be more intense with inflammation, as in this example.

Schuster et al. J Nucl Med 2014;55:1986-92.

Incidental Uptake and Variants

- Incidental non-physiologic uptake can occur



Tubulovillous adenoma with atypia

Schuster et al. J Nucl Med 2014;55:1986-92.

Reading Assignment

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Anti-1-Amino-3-^{18}F-Fluorocyclobutane-1-Carboxylic Acid: Physiologic Uptake Patterns, Incidental Findings, and Variants That May Simulate Disease

David M. Schuster[1], Cristina Nanni[2], Stefano Fanti[2], Shuntaro Oka[3], Hiroyuki Okudaira[3], Yusuke Inoue[4], Jens Sörensen[5], Rikard Owenius[6], Peter Choyke[7], Baris Turkbey[7], Trond V. Bogsrud[8,9], Tore Bach-Gansmo[8], Raghuveer K. Halkar[1], Jonathon A. Nye[1], Oluwaseun A. Odewole[1], Bital Savir-Baruch[1], and Mark M. Goodman[1]

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Anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid (^{18}F-FACBC) is a synthetic amino acid analog PET radiotracer undergoing clinical trials for the evaluation of prostate and other cancers. We aimed to describe common physiologic uptake patterns, incidental findings, and variants in patients who had undergone ^{18}F-FACBC PET.

Key Words: ^{18}F-FACBC; physiologic uptake; positron emission tomography

J Nucl Med 2014; 55:1986–1992
DOI: 10.2967/jnumed.114.143628

Schuster et al. J Nucl Med 2014;55:1986-92.

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Sample Axumin Interpretation Report

Sample Axumin® (Fluciclovine F 18) Interpretation Report

This resource can assist with providing appropriate information regarding your patient's Axumin (fluciclovine F 18) scan. It is not a guide or instructions, nor is it intended to replace the independent medical judgment of the provider. Blue Earth Diagnostics does not provide nor imply any medical advice regarding patient care or patient management. It is the provider's responsibility to accurately complete and submit necessary information.

Note: Text in *italics* denotes suggested information to record.

- **DIAGNOSIS:** *Consider including stage and state of prostate cancer.*
- **EXAMINATION:** *PET/CT or PET/MRI*
- **EQUIPMENT:** *PET camera (make & model)*
- **AGENT:** Fluciclovine F 18
- **HISTORY:** *Consider including the following: Clinical question; date of diagnosis; prior treatment (e.g. prostatectomy, radiation therapy, other locoregional treatment, hormonal therapy, chemotherapy, other systemic treatments); current treatment; current/recent PSA levels [showing suspicion of recurrence; PSA doubling time (or comment if this is not available)]; Gleason Score (initial); prior imaging/correlative studies, notable clinical symptoms (e.g. pain; loss of ROM).*

1. Axumin® (fluciclovine F 18) Injection; US Prescribing Information; Blue Earth Diagnostics, Ltd.
2. Axumin® (fluciclovine F 18) Imaging & Interpretation Manual (Prostate Cancer) v2.0.

Sample Axumin® (Fluciclovine F 18) Interpretation Report

- **PROCEDURE:** *Consider including the following: Administered activity; injection site (right or left); oral or i.v. contrast (if applicable); extravasation/tracer retention (if applicable); patient compliance with recommended scan preparation (i.e. exercise, fasting, voiding); time of injection.*
- **ACQUISITION:** *Consider including the following: Uptake time; axial extent of scan; minutes per bed position.*
- **FINDINGS:** *Consider including the following: Any findings, with reference to the following regions: local recurrence; loco-regional recurrence; distant disease; focality, size and image slice number of any abnormal findings and describe abnormal uptake relative to blood pool and bone marrow; normal findings; muscle uptake; liver uptake; pancreas uptake; incidental findings; SUV_{max} (lesion); SUV_{mean} (background).*

  Consider using terms like uptake, activity, avidity, or accumulation. Consider avoiding terms like "metabolic" or "hypermetabolism".

  Consider including images/snapshots of findings.

  IMPRESSION: *Consider recording an abbreviated summary of relevant findings and if possible, answer clinical question.*
- **RECOMMENDATIONS:** *Consider including the following: additional testing, clinical correlation.*

1. Axumin® (fluciclovine F 18) Injection; US Prescribing Information; Blue Earth Diagnostics, Ltd.
2. Axumin® (fluciclovine F 18) Imaging & Interpretation Manual (Prostate Cancer) v2.0.

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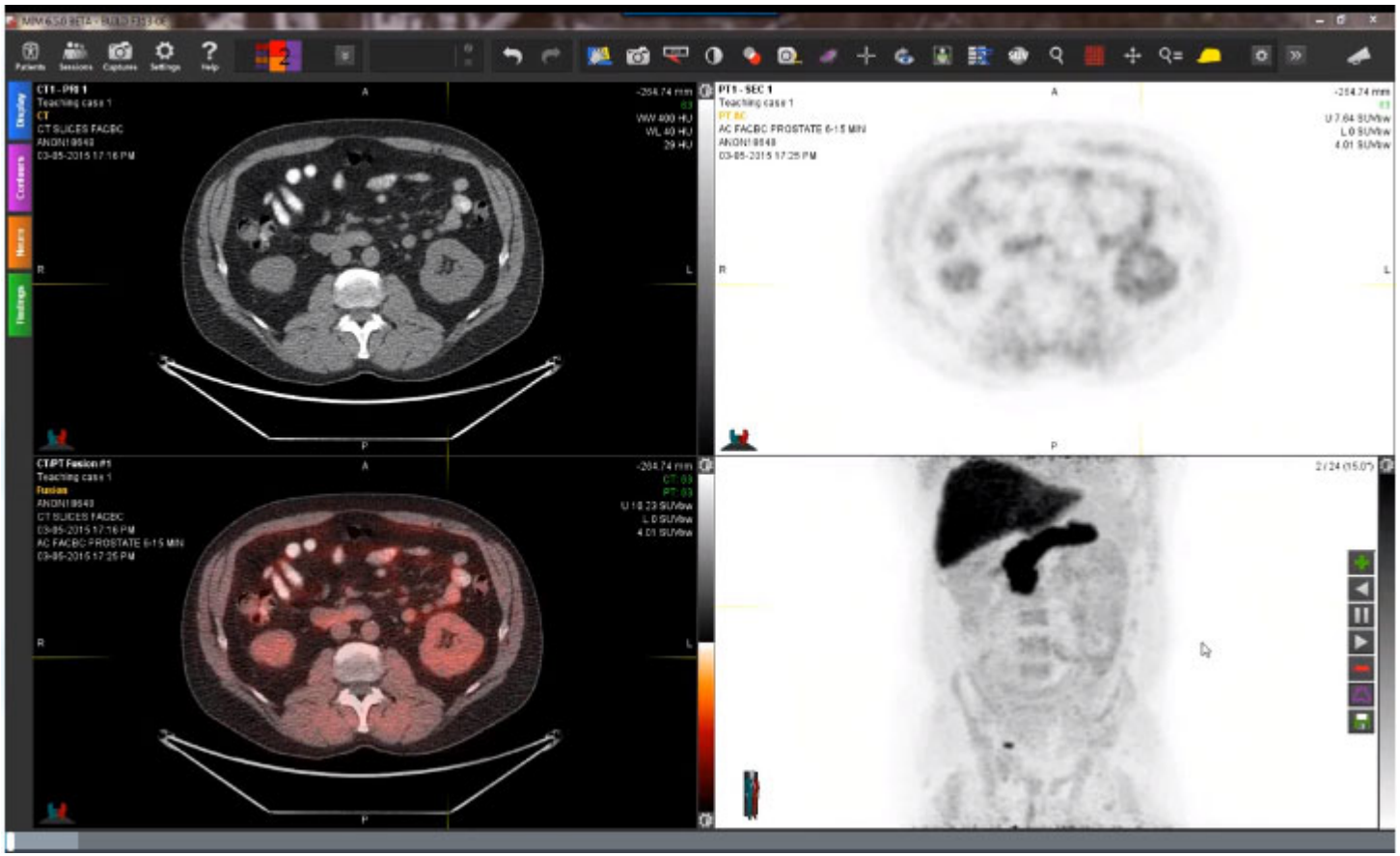
Case Studies

Case 1: Review Video: Click to Play

- Post robotic-assisted laparoscopic radical prostatectomy and bilateral staging pelvic lymphadenectomy
- Now rising PSA to 0.41 ng/mL



Case 1: Summary

- Post robotic-assisted laparoscopic radical prostatectomy and bilateral staging pelvic lymphadenectomy
- Now rising PSA to 0.41 ng/mL

Findings:

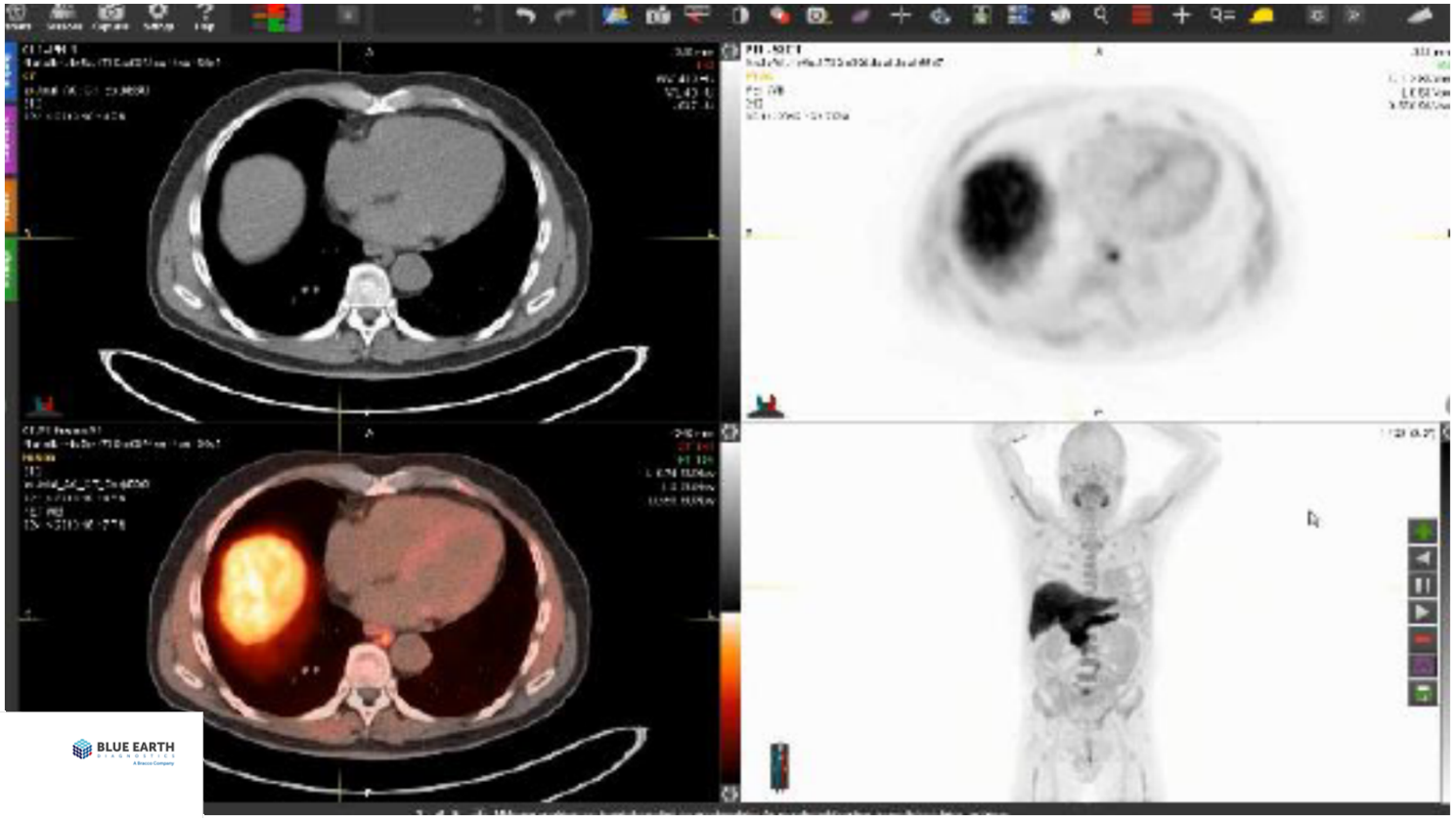
- Single intense right internal iliac/pelvic side wall node (1 cm), consistent with metastasis.
- No uptake in prostate bed.
- Symmetric mild uptake in negative inguinal nodes.
- Bilateral benign lymphoceles.
- Otherwise negative.

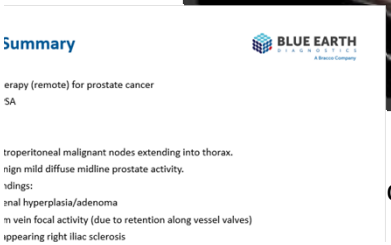
Case 2: Review Video: Click to Play

- Post-radiotherapy (remote) for prostate cancer
- Now rising PSA

Errata (video narration): Node referred to as “hot and benign” but should be “hot and malignant”

Also, tool keyboard shortcuts may change over time depending on software version, but may be customized





cs 2019.

Case 2: Summary

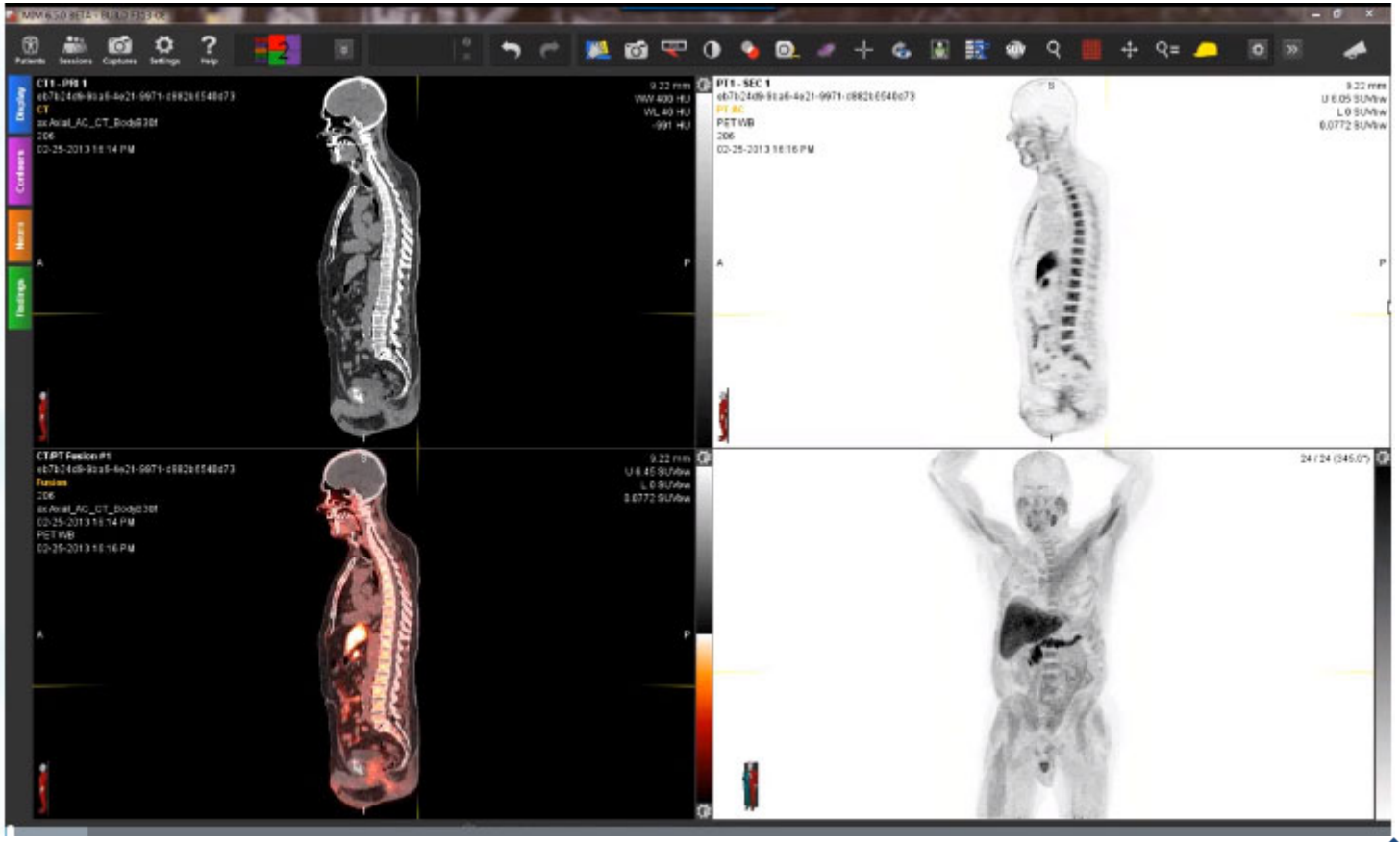
- Post-radiotherapy (remote) for prostate cancer
- Now rising PSA

Findings:

- Extensive retroperitoneal malignant nodes extending into thorax.
- Probable benign mild diffuse midline prostate activity.
- Incidental findings:
  - Left adrenal hyperplasia/adenoma
  - Right arm vein focal activity (due to retention along vessel valves)
  - Benign appearing right iliac sclerosis

Case 3: Review Video: Click to Play

- Post-radiotherapy and ADT
- Now rising PSA
- Negative MR



Case 3: Summary

- Post-radiotherapy and ADT
- Now rising PSA
- Negative MR

Findings:

- Right apex hot focus in mild diffuse background.
- Negative nodes, bone.
- Physiologic muscle, bladder tracer jets (percolation).

Follow-up

- Biopsy positive right apex.
- Salvage brachytherapy; PSA nadir <0.2 ng/ml.

Case 4: Review Video: Click to play

- Post radical prostatectomy, pT3, Gleason 9
- PSA post-op 1.1 ng/ml
- Axumin® scan 5 months later

Case 4: Summary

- Post radical prostatectomy, pT3, Gleason 9
- PSA post-op 1.1 ng/ml
- Axumin® scan 5 months later

Findings:

- L3 sclerotic hot focus.
- Post-op bladder tracer activity.
- Incidental mucocele left maxillary sinus, right renal cysts.

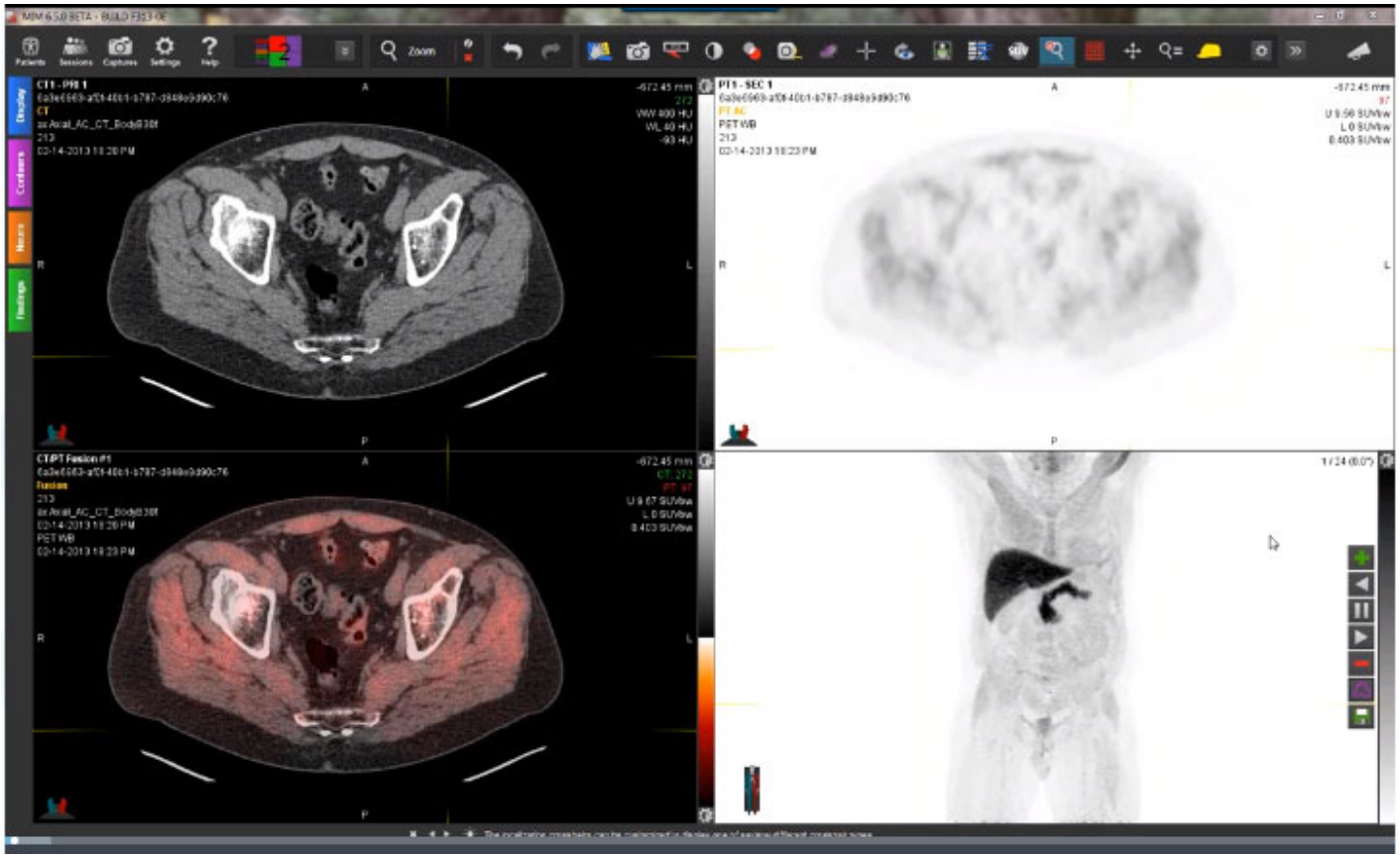
Follow-up:

- MR initially negative, then became positive at L3 and T12.
- Probably microscopic at T12 or spread later.

Case 5: Review Video: Click to Play

- Post radical prostatectomy, negative lymphadenectomy
- Now rising PSA to 0.73 ng/ml
- Negative MR for malignancy
- Earlier negative skeletal screening

Errata (video narration): In sacrum review, schwannoma referred to as “mucocele”



Case 5: Summary

- Post radical prostatectomy, negative lymphadenectomy
- Now rising PSA to 0.73 ng/ml
- Negative MR for malignancy
- Earlier negative skeletal screening

Findings:

- Intense small left presacral node 3 x 4 mm, measure SUV.
- Fluciclovine negative sclerotic lesions (T8, L1, L4, L5, left acetabulum, right ilium) needing evaluation. Review prior skeletal screening. Further imaging?
- Schwannoma right sacrum (confirmed on MR).
- Goitre
- Post-prostatectomy bladder
- Benign left lymphocele
- Mild symmetric inguinal nodal activity
- Sinus disease

Case 6: Review Video: Click to Play

- Radiation therapy for Gleason 7 prostate cancer; short course ADT
- Now rising PSA to 29.7 ng/ml
- Delayed acquisition (22 min) whole body

Case 6: Summary

- Radiation therapy for Gleason 7 prostate cancer; short course ADT
- Now rising PSA to 29.7 ng/ml
- Delayed acquisition (22 min)

Findings:

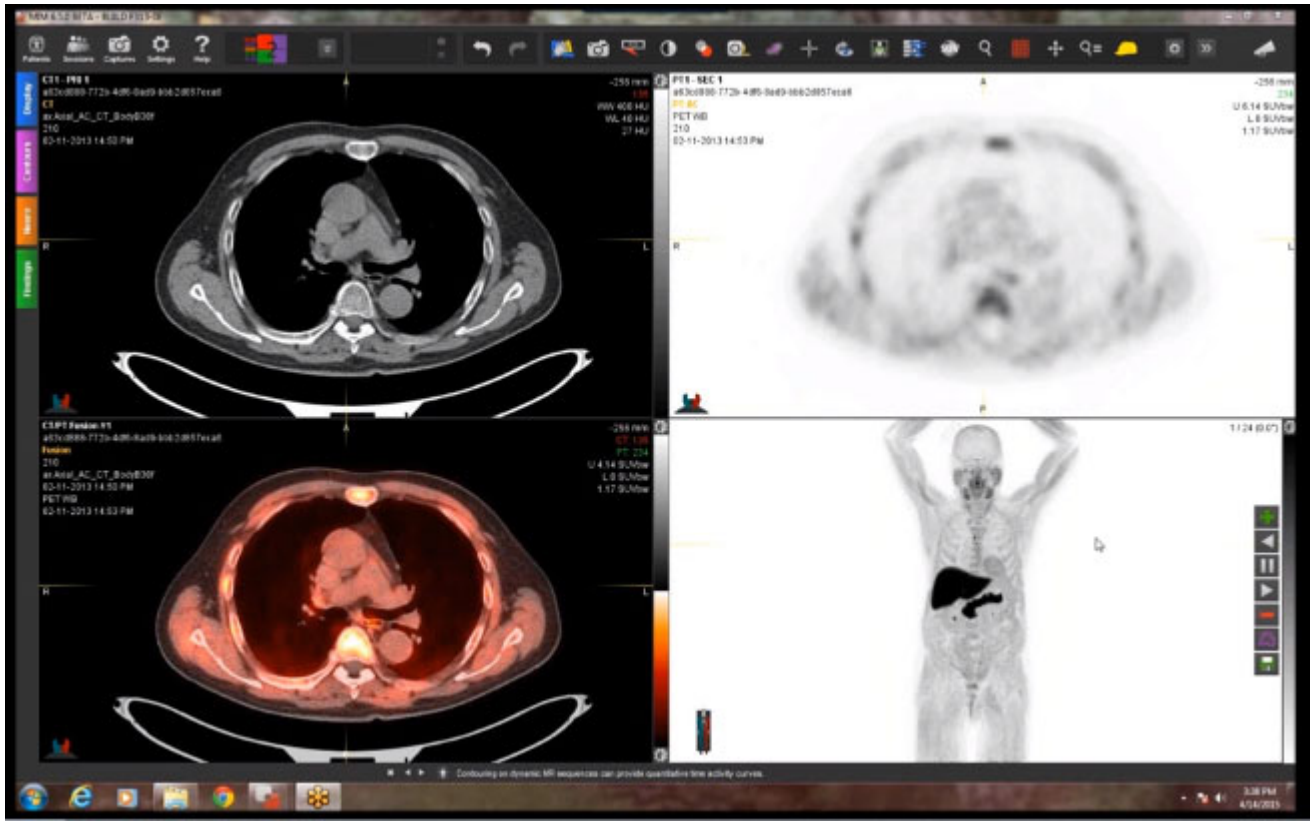
- Left lobe positive. Mild elsewhere, nonspecific.
- Bones suspicious at T9, L2, L3, right ilium with negative CT. Possible R femur. Further investigation especially since focal activity on delayed imaging.
- Nodes negative.

Follow-up:

- Biopsy positive left lobe; suspicious findings on MR at L2 and L3.

Case 7: Review Video: Click to Play

- Remote radiation therapy Gleason 8 cancer
- Negative subsequent pelvic node dissection
- Local relapse with Gleason 9, LHRH
- Rising PSA despite ADT
- PSA now 62 ng/ml



Case 7: Summary

- Radiation therapy Gleason 8 cancer
- Negative subsequent pelvic node dissection
- Local relapse with Gleason 9, LHRH
- Rising PSA despite ADT
- PSA now 62 ng/ml

Findings:

- Some urinary excretion with dependent activity in bladder.
- Mild-moderate heterogenous prostate right > left. Call positive since significantly greater than blood pool.
- Definitively positive precarinal and right paratracheal nodes.

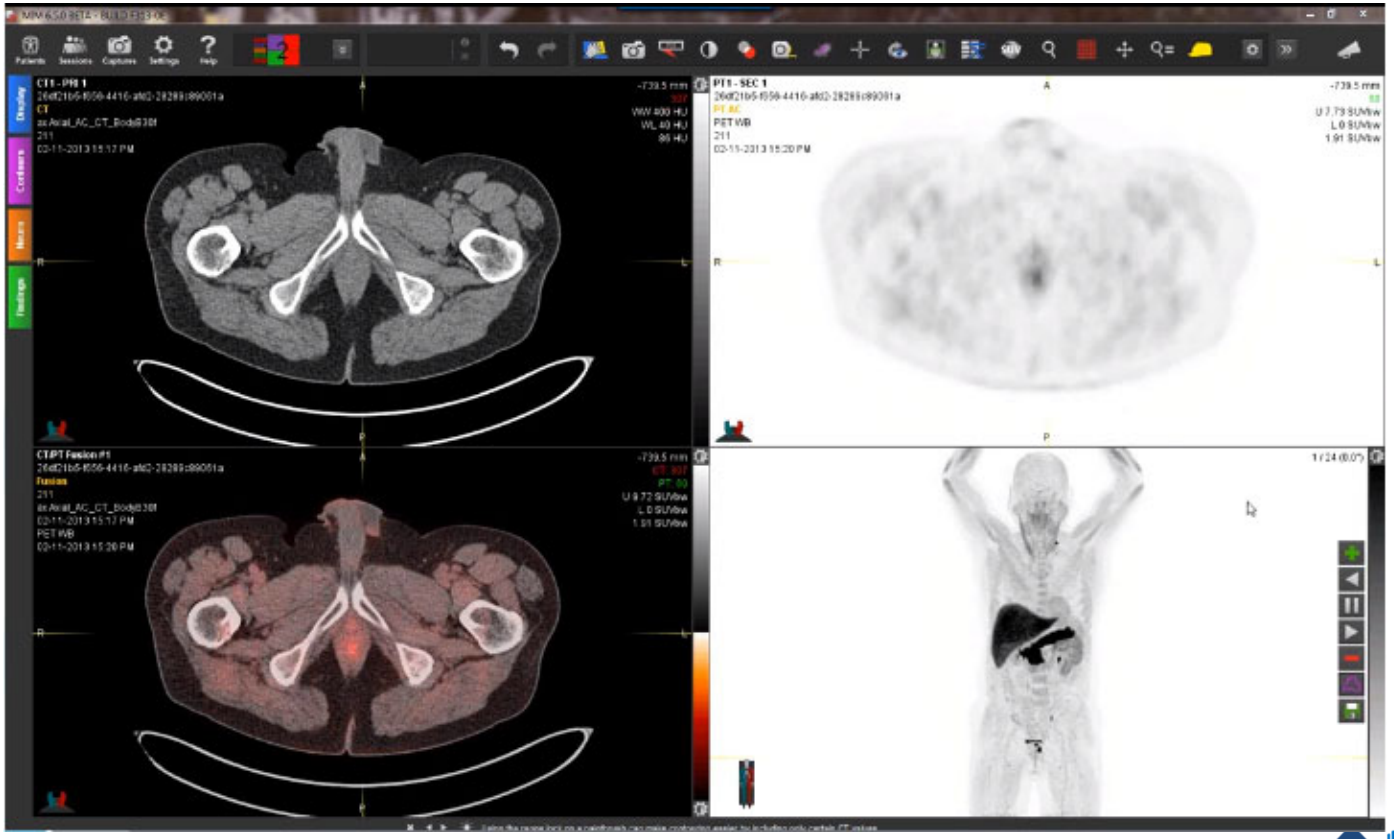
Follow-up:

- Nodes enlarged on subsequent CT; explanation for very elevated PSA.
- Prostate was not biopsied; may be seeing partially treated disease with known earlier recurrence.

Case 8: Review Video: Click to Play

- Prostate cancer T3b, N0M0 Gleason 9
- Radiotherapy and Goserelin then Bicalutamide
- Initial response on MR seen with reduction tumor size but relapse subsequently with enlarging tumor

Errata (video narration): Activity at “base of prostate” at one point referred to as “base of bladder”.



Case 8: Summary

- Prostate cancer T3b, N0M0 Gleason 9
- IMRT and Zoladex then Bicalutamide
- Initial response on MR seen with reduction of tumor size, but relapse subsequently with enlarging tumor

Findings:

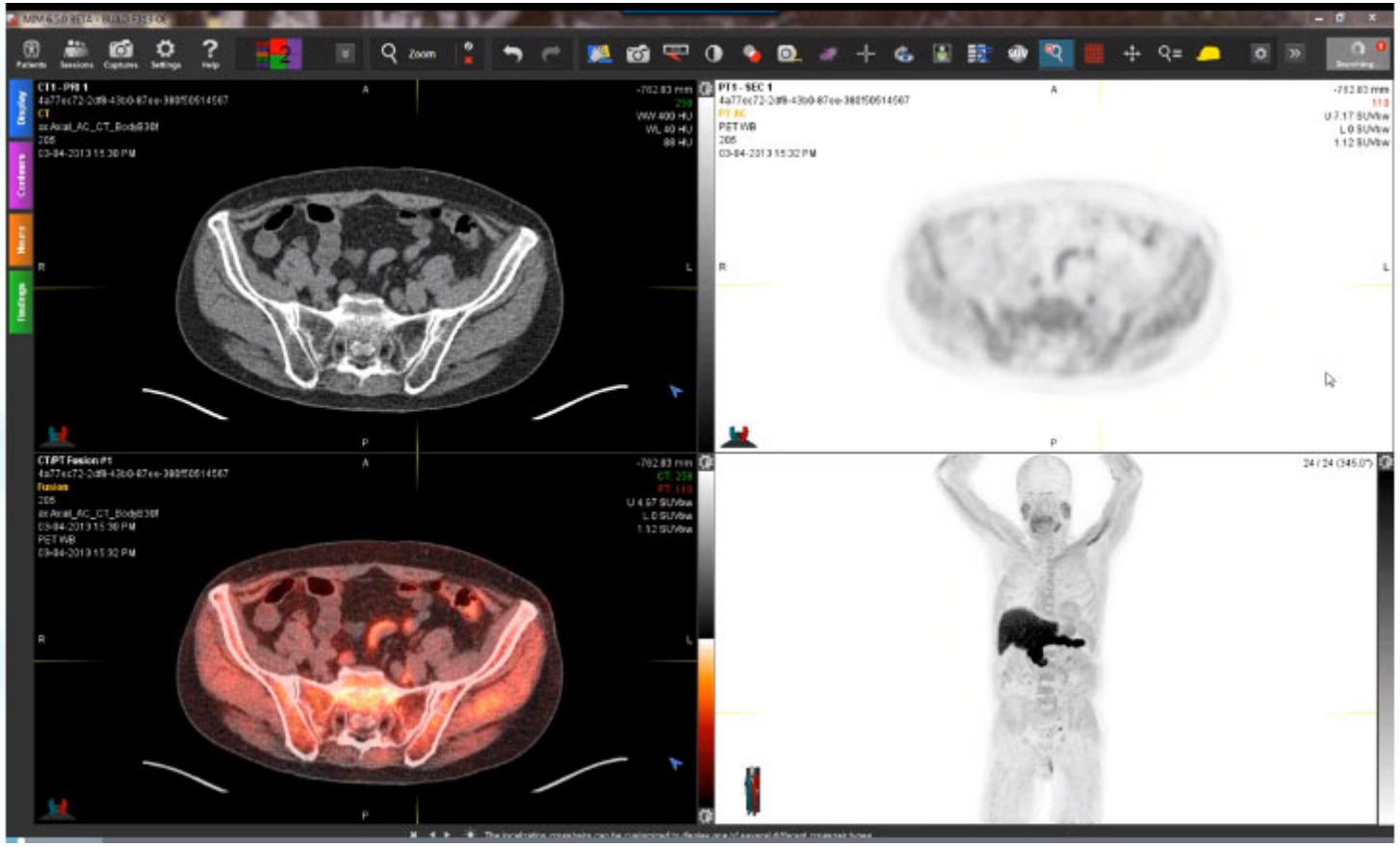
- Urinary activity in ureters and bladder.
- But also intense activity left prostate but activity at prostate base too; be suspicious, window and see it is separate, no TURP history.
- Benign inguinal nodes with no extraprostatic suspicious foci.
- Incidental activity left superficial neck, correlates with vessel: reflux into a collateral and holdup at valve.
- Gallstones with milk of calcium.

Follow-up:

- Salvage brachytherapy left lobe only. But tumor at base grew and invaded bladder wall.

Case 9: Review Video: Click to Play

- Radical prostatectomy Gleason 7, T3b, also affected right seminal vesicle
- Salvage radiation therapy
- Now PSA rise to 3.2



Case 9: Summary

- Radical prostatectomy Gleason 7, T3b, also affected right seminal vesicle
- Salvage radiation therapy
- Now PSA rise to 3.2

Findings:

- No suspicious activity in bed.
- Left sacral bone metastasis.
- 5-6 mm left common iliac near bifurcation node; activity similar to marrow but intense for size.
- Also, tiny 2-3 mm left obturator/external iliac mild uptake; may also be suspect in light of other disease but would not call positive in isolation.

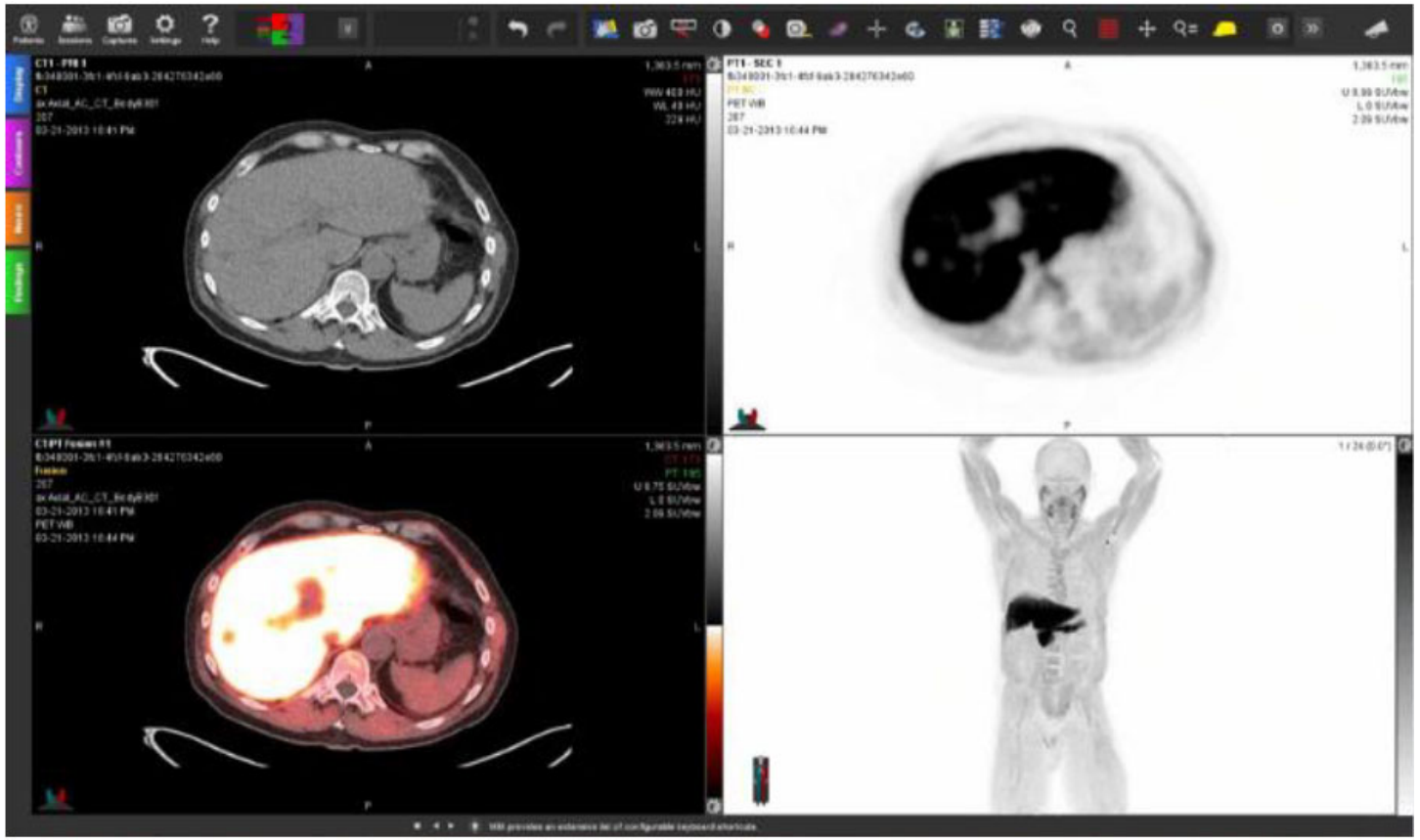
Follow-up:

- MR confirmed sacral metastasis; suspicious left iliac nodes (though not a proof).

Case 11: Review Video: Click to Play

- Radiation therapy Gleason 9, salvage prostatectomy 2012, neuroendocrine differentiation,
- Negative lymphadenectomy
- Now PSA 1.1

Errata (video narration): During L3 measurement, “representative vertebral body” was referred to as a “representative node” in error



Case 11: Summary

- Radiation therapy Gleason 9, salvage prostatectomy 2012, neuroendocrine differentiation
- Negative lymphadenectomy
- Now PSA 1.1

Findings:

- Axillary vein activity on left; Benign liver cyst/hemangioma.
- Indeterminate bed. Bulbous urethra equal to marrow at anastomosis, though not focal.
- Abnormal nodes:
  - Right paracaval at bifurcation. Left obturator/external iliac.
  - Subtle right external iliac node. Not called as positive alone, but suspect in this case.

Follow-up:

- No definitive level of proof. Radiation therapy to right paracaval and left obturator nodes, mild PSA response but then increased with unchanged appearance on CT of nodes.
- No bone disease on MR. On hormonal therapy, explanation may be right external iliac node, other microscopic disease or anastomotic recurrence.

Sources

Sources

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