

FLUCICLOVINE:

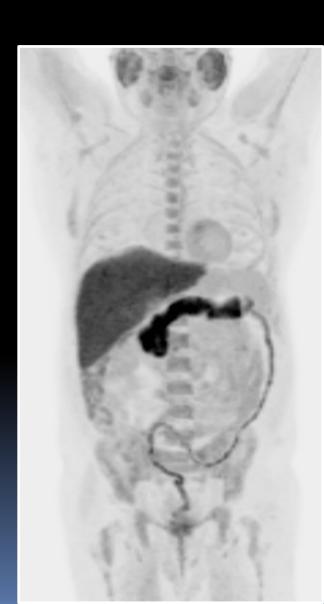
1ST FDA APPROVED F-18 PET IMAGING AGENT FOR RECURRENT PROSTATE CANCER

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I HAVE NO FINANCIAL DISCLOSURES.

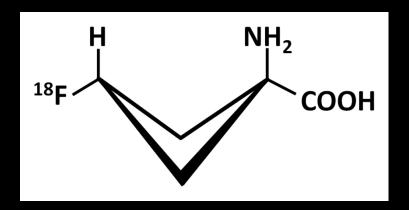
GOALS AND OBJECTIVES

- 1. Review characteristics and clinical pharmacology of Fluciclovine F-18.
- 2. Discuss role of Fluciclovine F-18 in management of prostate cancer and research supporting its efficacy.
- 3. Contrast administration & image acquisition of Fluciclovine F-18 to commonly utilized FDG.
- 4. Review interpretation criteria for Fluciclovine F-18 images in setting of suspected recurrent prostate cancer.



Anti-1-Amino-3-18F-Fluorocyclobutane-1-Carboxylic Acid (FACBC)

L-Leucine Amino Acid Analogue



- LEUCINE: essential amino acid for protein synthesis and cell growth
- Taken up via LAT & ASCT systems
- LAT & ASCT systems up regulated in many carcinomas
 - LAT1 and ASCT2 associated with more aggressive disease
- FACBC does not undergo metabolism
- Uptake in prostate-specific membrane antigen (PSMA) expressing and nonexpressing tumor cells

PERFORMANCE OF F-18 FACBC

- Efficacy initially evaluated by Emory University
- 105 F18-FACBC PET/CT scans compared to histopathology
- Interpreted by 3 blinded independent readers
- Detection rate 60% PSA <1.78
- Detection rate 80% PSA >1.78
- <10% extra-prostatic FP rate

	READER 1	READER 2	READER 3
PATIENT	N=104	N=105	N=99
TP	75	72	63
FP	24	23	13
TN	5	7	15
FN	0	3	8
PROSTATE BE	:D		
TP	58	56	47
FP	29	26	15
TN	10	12	24
FN	1	3	10
EXTRAPROST	ATIC		
TP	25	26	22
FP	2	2	2
TN	0	0	0
FN	1	0	1

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PATIENT

Sensitivity 95%
Specificity 31%
PPV 78%
NPV 71%

PROSTATE/BED

Sensitivity 92%
Specificity 40%
PPV 70%
NPV 77%

EXRAPROSTATIC

Sensitivity 97%
Specificity 0%
PPV 92%
NPV 0%

18F-FLUCICLOVINE PET-CT VS IN-111 CAPROMAB PENDETIDE SPECT-CT

Patients and methods:

- 93 patients with suspected recurrent prostate carcinoma
- Underwent 18F-Fluciclovine PET-CT &
 111In-capromab pendetide (Prostascint) SPECT-CT
- Both exams completed in 90 days
- Reference standards applied by multidisciplinary board

Results:

	PROSTATE/BED	TP	TN	FP	FN
•	FACBC	55	12	18	6
•	Capromab pendetide	41	17	13	20

	PROSTATE/BED	SENS	SPEC	ACC	PPV	NPV
•	FACBC	90%	40%	74%	75%	67%
•	Capromab pendetide	67%	57%	64%	76%	46%

[√] FACBC identified 14 more positive prostate bed recurrences (55 vs 41)

18F-FLUCICLOVINE PET-CT VS IN-111 CAPROMAB PENDETIDE SPECT-CT

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- Underwent 18F-Fluciclovine PET-CT &
 111In-capromab pendetide (Prostascint) SPECT-CT
- Both exams completed in 90 days
- Reference standards applied by multidisciplinary board

Results:

	EXTRAPROSTATIC	TP	TN	FP	FN
•	FACBC	22	29	1	18
•	Capromab pendetide	4	26	4	36

	EXTRAPROSTATIC	SENS	SPEC	ACC	PPV	NPV
•	FACBC	55%	97%	73%	96%	62%
•	Capromab pendetide	10%	87%	43%	50%	42%

- ✓ FACBC identified 18 more patients with extraprostatic involvement (22 vs 4)
- ✓ Correctly up-staged 18 of 70 cases (26%)
- √ Radiation exposure of FACBC was ~1/3 of Prostascint

18F-FLUCICLOVINE VS 11C-CHOLINE PET/CT

Choline: Marker of lipogenesis; enters cell and catalyzed by choline kinase (up-regulated in PCa) to phosphorylcholine then phosphatidylcholine in cell membrane.

Patients and methods:

- Fifteen patients radically treated for prostate cancer
- Presented with rising PSA levels, median PSA 1.44 ng/mL
- Underwent (11)C-choline PET/CT & (18)F-fluciclovine PET/CT within 1 week

Results:

- (18)F-fluciclovine significantly superior to (11)C-choline
 - Patient-based analysis AND
 - Lesion-based analysis; lymph nodes, bone, & local relapse
- ✓ Superior performance of FACBC at low, intermediate, and high PSA levels

C11-CHOLINE POS 3/15 PTs \rightarrow 20%

F18-FACBC
POS 6/14 PTs → 40%

C11-CHOLINE
DETECTED 6 LESIONS
4 BONE, 1 LN, 1 LOCAL

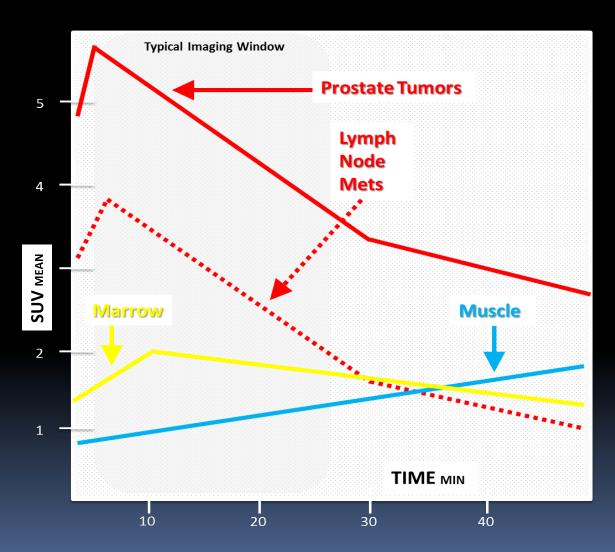
F18-FACBC
DETECTED 11 LESIONS
5 BONE, 5 LN, 1 LOCAL
TO INCLUDE ALL 6
SEEN ON C11

BIODISTRIBUTION



- PANCREAS > LIVER most intense uptake
- Moderate salivary & pituitary uptake
- Variable mild to moderate bowel activity
- Moderate red marrow & mild MUSCLE activity present early (<15 min)
 - Marrow activity
 ↓ while MUSCLE activity
 ↑ with time
- Lungs have little to no uptake
- <u>In contrast to FDG</u>:
 - Minimal to no brain uptake
 - Little RENAL excretion
 - Mild activity may accumulate in BLADDER, but not to degree that interferes with interpretation

PHARMACOKINETICS



→ In contrast to FDG:

FACBC uptake in prostate cancer & lymph node mets peaks early @ 4-10 min

VERSUS

FDG peaks @ 90+ min most tumors

61%
 Uptake of FACBC by prostate cancer lesions @ 90 min

GIVEN THIS, imaging begins

3-5 min post injection FACBC

VERSUS

45-90 min for FDG

PROTOCOL

FACBC (Fluciclovine)

- Withhold voiding x30 min prior
- Perform injection with patient on PET-CT scanner bed in supine position
- Immediately reposition arms above head
- 1-2 min after injection, initiate CT
- Begin PET scan 3-5 min after injection
 - ► Tumor-to-normal tissue contrast is highest 4-10 min after injection
 - ► 61% **U** tumor uptake by 90 min

If acquisition started too early, increased blood pool may be encountered
If acquisition started too late, increased muscle uptake typically present

INTERPRETATION CRITERIA

PROSTATE BED AND PROSTATE GLAND

Avidity of pathologic FACBC uptake assessed visually

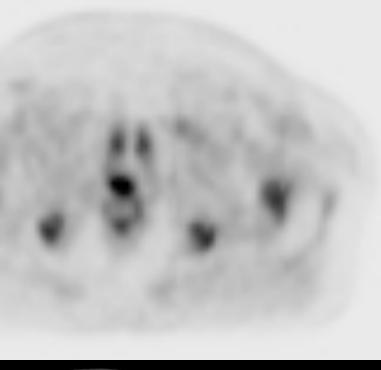
Prior Prostatectomy

- Focal avidity ≥ bone marrow is suspicious for cancer.
 - o BUT if focus of avidity small (<1cm), suspicious if >> blood pool.

Non-Prostatectomy

- Focal asymmetric ≥ bone marrow is suspicious for recurrence.
 - o BUT if focus of uptake small (<1cm), suspicious if >> blood pool.
 - → Focal median lobe uptake has high likelihood of FP.
- Diffuse uptake >> bone marrow is moderately suspicious for recurrence

Manufacturer recommends review of PET only coronal images to aid interpretation.

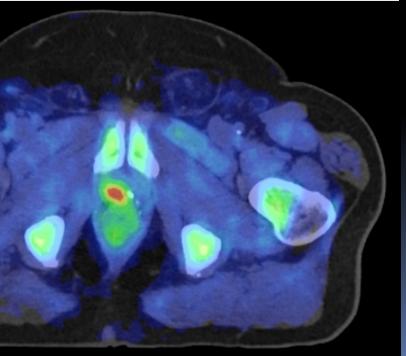


PATHOLOGIC UPTAKE

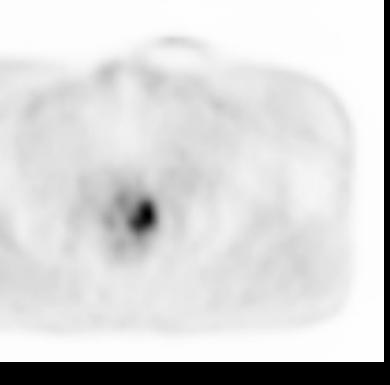
PROSTATE BED, PROSTATECTOMY

66 YO S/P PROSTATECOMY WITH BCR

- ► FOCAL UPTAKE
- ► ≥ 1 CM IN SIZE
- ► VISUALLY ≥ BONE MARROW
- ✓ SUSPICIOUS FOR CANCER RECURRENCE





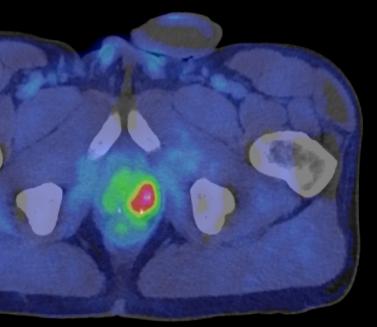


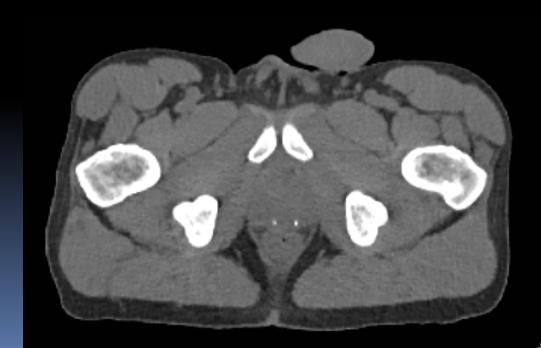
PATHOLOGIC UPTAKE

NON-PROSTATECTOMY

62 YO S/P XRT WITH BIOCHEMICAL RECURRENCE (BCR)

- ► FOCAL ASYMMETRIC UPTAKE
- ► ≥ 1 CM IN SIZE
- ► VISUALLY ≥ BONE MARROW
- ✓ SUSPICIOUS FOR CANCER RECURRENCE



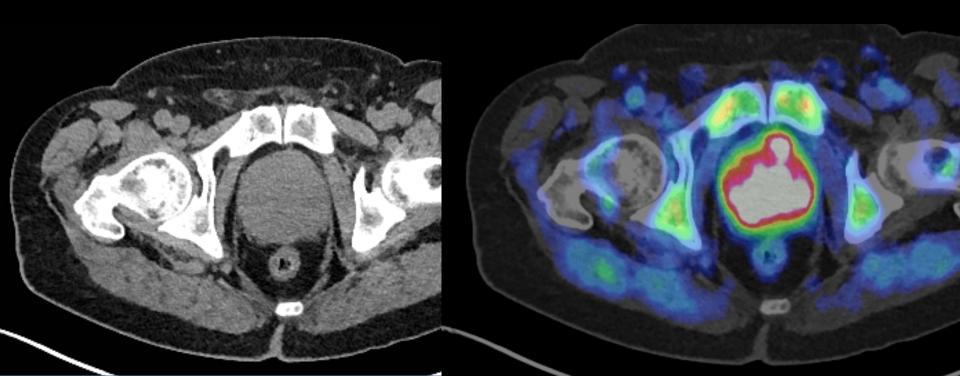


DIFFUSE UPTAKE

NON-PROSTATECTOMY

66 YO S/P XRT WITH BCR

- ► DIFFUSE UPTAKE
- ► VISUALLY >> BONE MARROW
- ✓ SUSPICIOUS FOR CANCER RECURRENCE



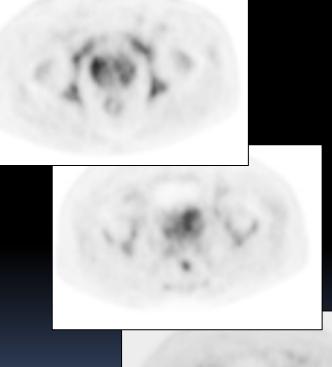
HETEROGENOUS OR MULTIFOCAL UPTAKE

NON-PROSTATECTOMY

58 YO S/P XRT WITH BCR

- ► HETEROGENOUS UPTAKE
- ► VISUALLY ≥ BONE MARROW
- ✓ SUSPICIOUS FOR CANCER RECURRENCE





18F-FLUCICLOVINE PET-CT FOR PRIMARY PROSTATE CANCER?

Schuster, AJNMMI 2013

- Correlated uptake of anti-3-[18F]
 FACBC with histology of prostatectomy specimens
- 10 patients
- Average SUVmax tumor 4.0 +/- 1.3
 - BUT nonmalignant 3.4 +/- 0.9

→ SIGNIFICANT OVERLAP OF AVIDITY FOR PCa VS NONMALIGNANT TISSUE

Turkbey, Radiology 2014

- Compared FACBC PET to MRI and Histology
- 21 patients with tumors > 0.5 cm
- Average SUVmax tumor 4.5 +/- 0.6
 - 2.8 +/- 0.5 normal prostate
 - BUT 4.3 +/- 0.7 BPH

→ NO DIFFERENCE PCa VS BPH

T2-weighted MR	ADC maps of DW MR	¹⁸ F FACBC PET/CT
Sensitivity 73%	Sensitivity 73%	Sensitivity 67%
Specificity 79%	Specificity 80%	Specificity 66%
PPV 66%	PPV 68%	PPV 50%
NPV 87%	NPV 87%	NPV 78%

INTERPRETATION CRITERIA

LYMPH NODES

Avidity of pathologic FACBC uptake assessed visually

<u>Sites Typical for Prostate Cancer Recurrence</u>

- Avidity ≥ bone marrow considered suspicious.
 - o *BUT* if node is small (<1cm) and in site typical for recurrence, may still consider suspicious if >> than blood pool

Atypical Sites (inguinal, distal external iliac, hilar, and axillary nodes)

- Mild, symmetric uptake is typically physiologic
 - o BUT if uptake present in context of other clear malignant disease, it may be considered suspicious for cancer recurrence.

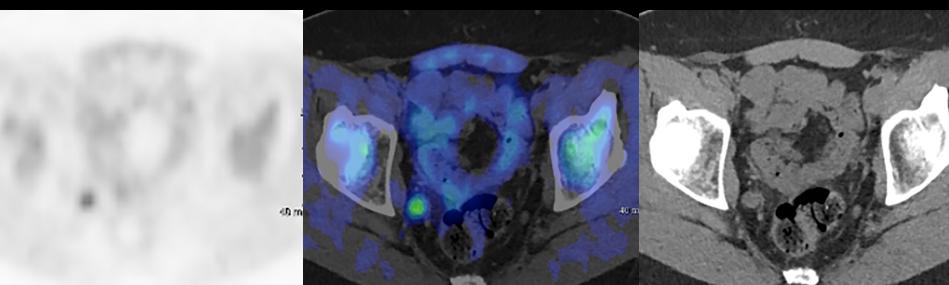


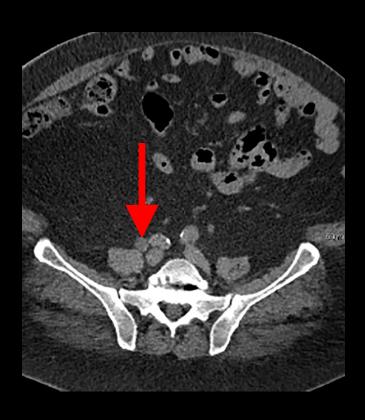
SUSPICIOUS NODAL UPTAKE

ASYMMETRIC LYMPH NODE AVIDITY

69 YO WITH HISTORY OF PROSTATE CANCER

- ► NODES TYPICAL FOR PROSTATE CANCER SPREAD
- ► ≥ 1 CM IN SIZE
- ► VISUALLY ≥ BONE MARROW
- ✓ SUSPICIOUS FOR CANCER RECURRENCE





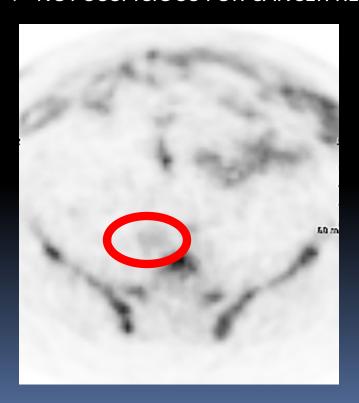
IF < 1 CM IN SIZE

- ► NODES TYPICAL FOR PROSTATE CANCER SPREAD
- ► VISUALLY NOT >> BLOOD POOL & NOT APPROACHING BONE MARROW
- **✗** SUSPICIOUS FOR CANCER RECURRENCE

BENIGN NODAL UPTAKE

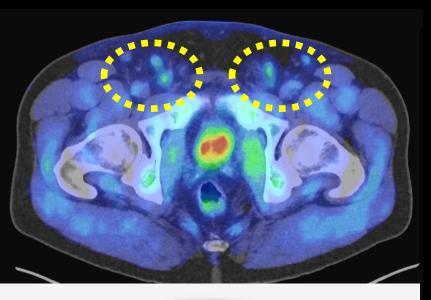
MILD LYMPH NODE AVIDITY

- ► NODES TYPICAL FOR PROSTATE CANCER SPREAD
- ►>= 1 CM IN SIZE
- ► VISUALLY < BONE MARROW
- **✗** NOT SUSPICIOUS FOR CANCER RECURRENCE



BENIGN NODAL UPTAKE

ATYPICAL SYMMETRIC LYMPH NODE AVIDITY



- ► ATYPICAL LN SITES FOR RECURRENCE INGUINAL DISTAL EXTERNAL ILIAC HILAR AXILLARY
- ► MILD TO MODERATE SYMMETRIC UPTAKE
- **✗** NOT SUSPICIOUS FOR CANCER RECURRENCE



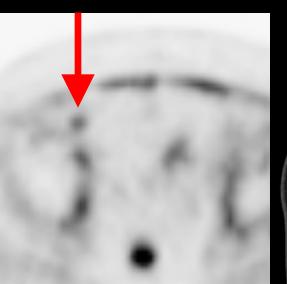
MODERATE PHYSIOLOGIC FACBC ACTIVITY IN BLADDER IS ATYPICAL. OCCURS IN 10-15% OF PATIENTS. MAY THEORETICALLY BE REDUCED BY NOT HAVING PATIENT VOID WITHIN 30 MIN BEFORE ADMINISTERING RADIOTRACER.

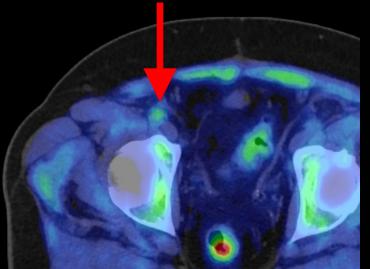
SUSPICIOUS NODAL UPTAKE

ISOLATED ASYMMETRIC LYMPH NODE AVIDITY

65 YO WITH PRIOR PROSTATECTOMY AND BCR

- ► ATYPICAL NODAL SITE FOR RECURRENCE: DISTAL EXTERNAL ILIAC
- ► ASYMMETRIC UPTAKE (INTENSITY DEPENDENT UPON SIZE)
- ► CAUSES OF FALSE POSITIVITY EXCLUDED: RECENT PROCEDURE OR IPSILATERAL HARDWARE/GRAFTS
- ✓ MODERATLEY SUSPICIOUS FOR CANCER RECURRENCE





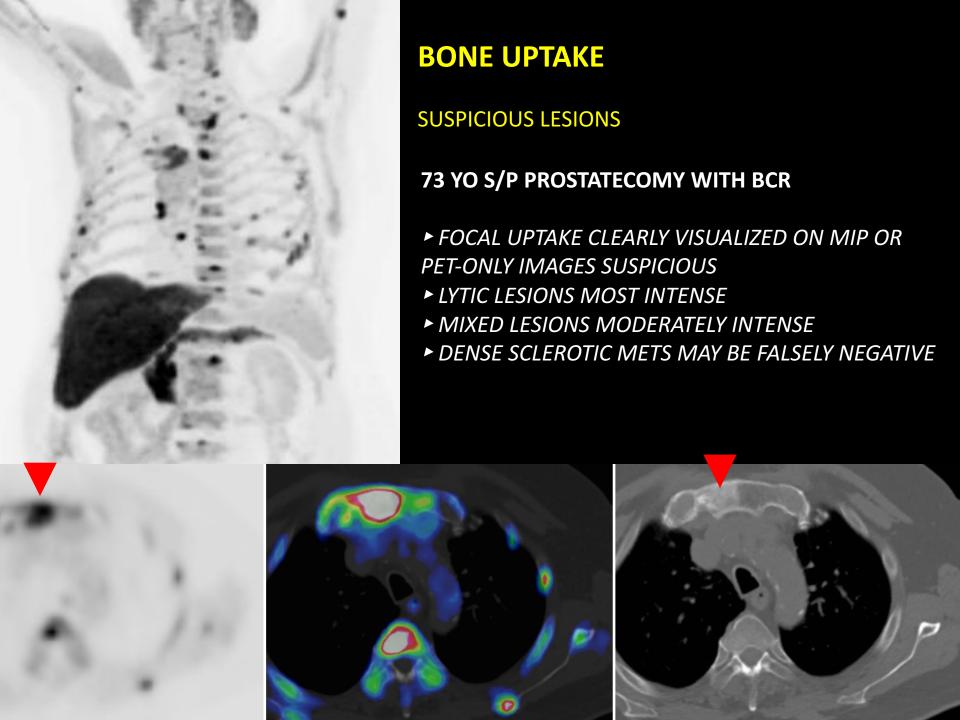


INTERPRETATION CRITERIA

BONE

Focal uptake CLEARLY visualized on Maximum Intensity Projection (MIP) or PET-only images, can be considered suspicious for cancer.

- o Lytic metastases typically show intense FACBC avidity
- o Mixed bony lesions most commonly show moderate uptake
- o Dense sclerotic abnormality on CT without uptake does not exclude metastasis
 - Alternative imaging should be considered

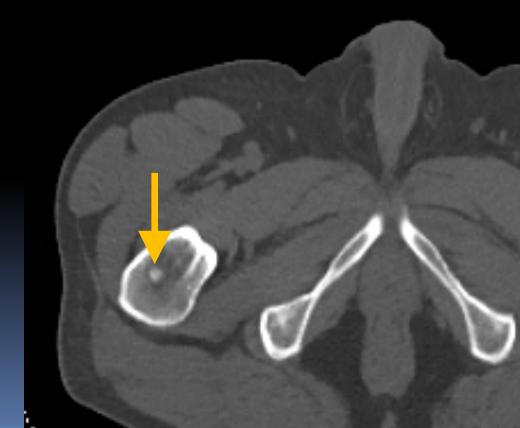




INDETERMINATE SCLEROTIC BONE LESION

58 YO S/P PROSTATECOMY WITH BCR

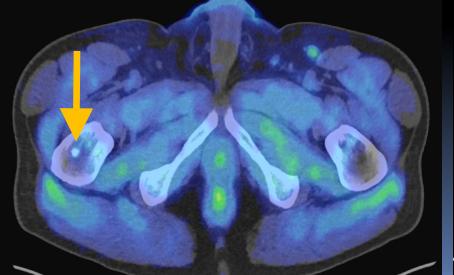
- 9 MM SCLEROTIC LESION IN RIGHT FEMUR
- REMAINDER OF EXAM NEGATIVE

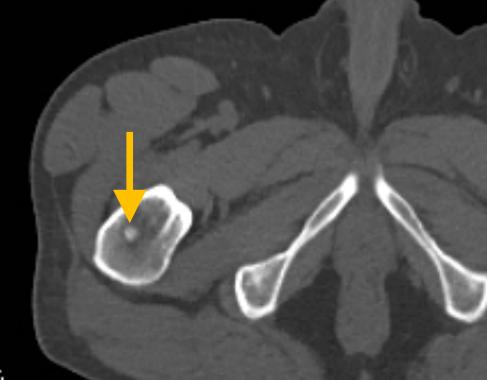


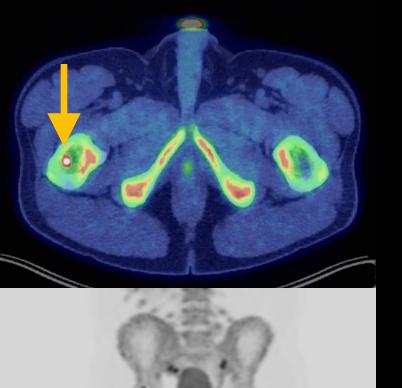
INDETERMINATE SCLEROTIC BONE LESION



- ► FOCAL UPTAKE CLEARLY VISUALIZED ON MIP OR PET-ONLY IMAGES SUSPICIOUS
- ► LYTIC LESIONS MOST INTENSE
- ► MIXED LESIONS MODERATELY INTENSE
- ► DENSE SCLEROTIC METS MAY BE FALSELY NEGATIVE



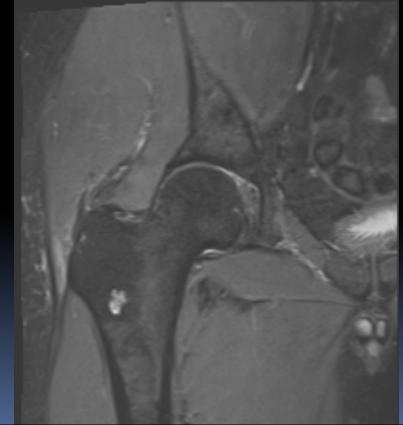




INDETERMINATE SCLEROTIC BONE LESION

► DENSE SCLEROTIC ABNORMALITY ON CT WITHOUT UPTAKE DOES NOT EXCLUDE METASTASIS

■ ALTERNATIVE IMAGING SHOULD BE CONSIDERED



POTENTIAL SOURCES OF FALSE POSITIVES

18F-FACBC has elevated uptake in numerous malignancies:

- Breast cancer
- Lung carcinoma
- Malignant and premalignant colonic neoplasia
- Squamous cell carcinoma of scalp
- Follicular lymphoma
- Multiple myeloma
- Primary and metastatic brain tumors

18F-FACBC also shows elevated uptake in benign tumors:

 Pituitary adenoma, meningioma, osteoid osteoma, and adrenal adenoma have been described.

POTENTIAL SOURCES OF FALSE POSITIVES

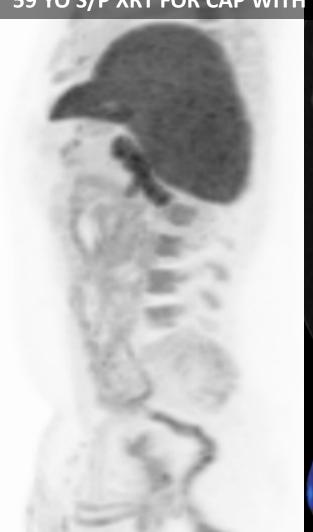
18F-FACBC also shows elevated uptake in inflammation:

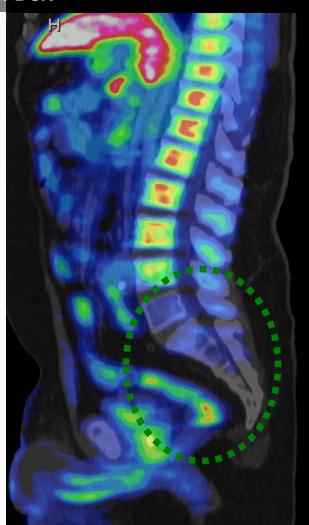
- Mild to moderate linear esophageal uptake in >50% of patients
- Other acute and chronic inflammation and infection:
 - Hilar, axillary, and inguinal lymph nodes
 - Inflammatory skin lesions, ringworm infection, and muscle inflammation
 - Mild uptake in degenerative facet disease
 → intensity generally < than 18F-FDG.



XRT CHANGES TO MARROW UPTAKE OF FACBC

59 YO S/P XRT FOR CAP WITH BCR







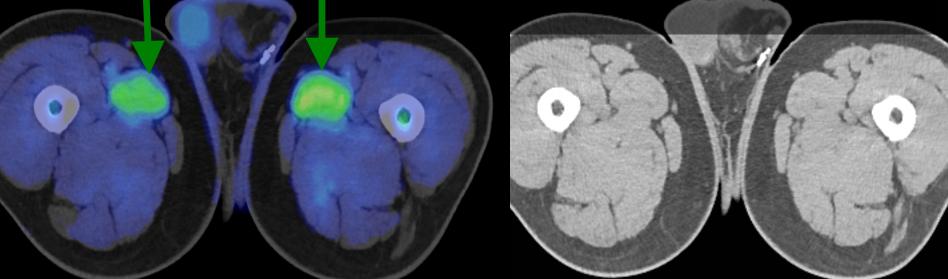


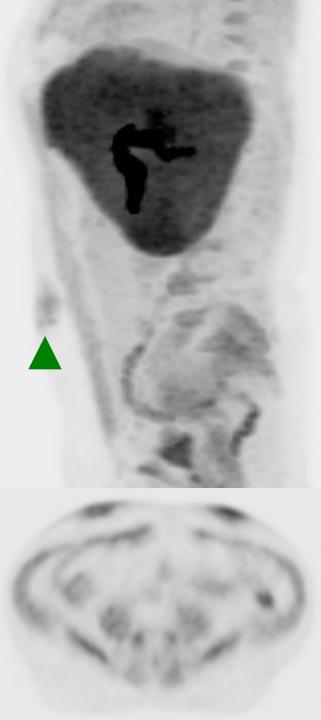
BENIGN INCREASED MUSCLE UPTAKE OF FACBC SECONDARY TO EXERCISE

59 YO S/P PROSTATECTOMY FOR CAP WITH BCR

► MILD DIFFUSE HOMOGENEOUS MUSCLE UPTAKE IS NORMAL & INCREASES WITH TIME AFTER INJECTION

► MODERATE TO INTENSE UPTAKE IS OFTEN SEEN IN SOFT TISSUE INFLAMMATION

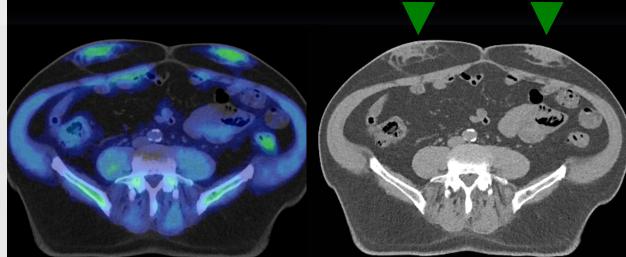




FACBC UPTAKE SECONDARY TO SOFT TISSUE INFLAMMATION RELATED TO INSULIN INJECTIONS

55 YO S/P PROSTATECTOMY FOR CAP WITH BCR

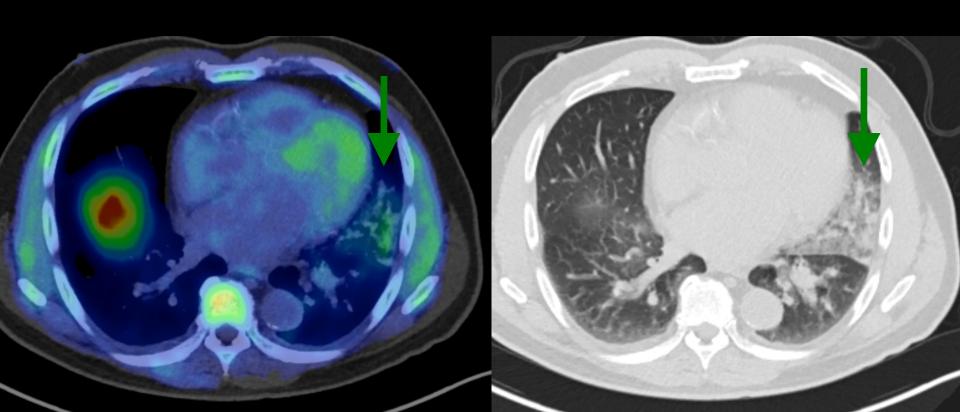
► MODERATE TO INTENSE UPTAKE IS OFTEN SEEN IN SOFT TISSUE INFLAMMATION

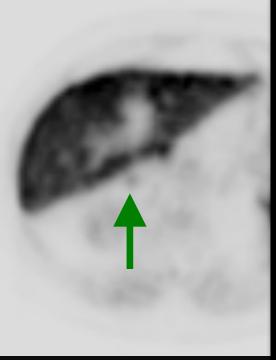


FACBC UPTAKE SECONDARY TO PNEUMONIA

62 YO S/P PROSTATECTOMY FOR CAP WITH BCR

MODERATE TO INTENSE UPTAKE IS OFTEN SEEN IN INFLAMMATION



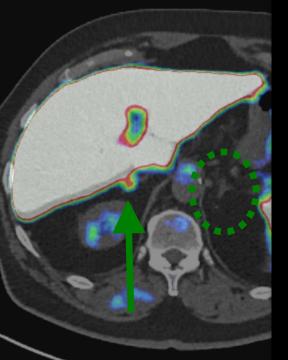


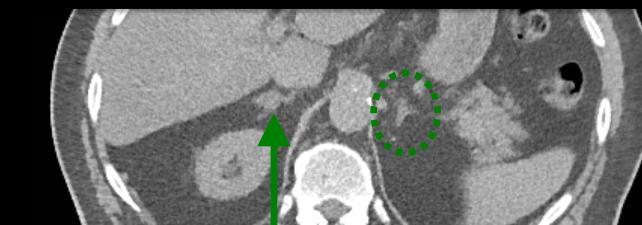


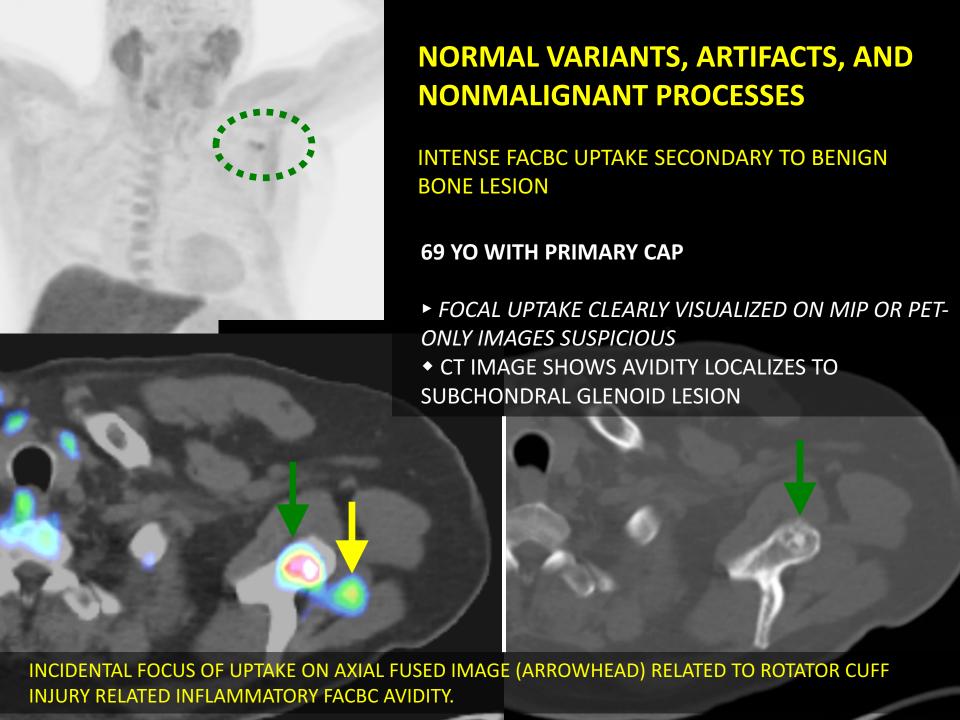
BENIGN INCREASED UPTAKE OF FACBC RELATED TO ADRENAL ADENOMA

62 YO S/P PROSTATECTOMY FOR CAP WITH BCR

- 18F-FACBC PET SHOWS SMALL FOCUS OF MILD INCREASED RADIOTRACER JUST POSTERIOR TO LIVER (ARROWHEAD).
- AXIAL CT IMAGE SHOWS AVIDITY LOCALIZES TO ADRENAL NODULE WITH ATTENUATION AND LONG TERM STABILITY CONSISTENT WITH BENIGN ADENOMA
- CONTRALATERAL NORMAL ADRENAL WITHOUT UPTAKE



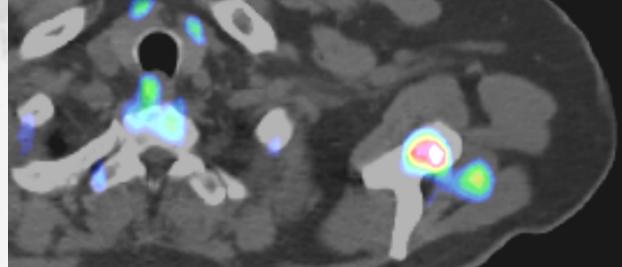


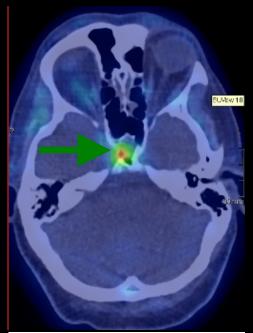


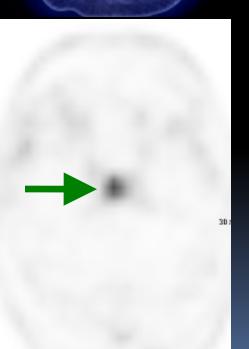


INTENSE FACBC UPTAKE SECONDARY TO BENIGN BONE LESION

- ◆ MDP BONE SCAN SHOWS OSTEOBLASTIC ACTIVITY AT SITE OF LESION IN ADDITION TO OTHER AREAS OF DEGENERATIVE UPTAKE
- ◆ NO FEATURES OF BONY METASTASES
- ► MILD FOCAL UPTAKE MAY BE SEEN IN DEGENERATIVE DISEASE, BUT USUALLY NOT TO SAME DEGREE AS WITH FDG.







BENIGN FOCAL AVIDITY FROM NORMAL PITUITARY GLAND UPTAKE

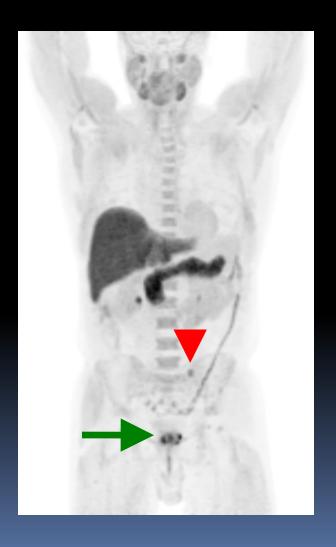
59 YO S/P XRT FOR CAP WITH BCR

► MODERATE PITUITARY GLAND UPTAKE IS PART OF THE NORMAL FACBC BIODISTRIBUTION

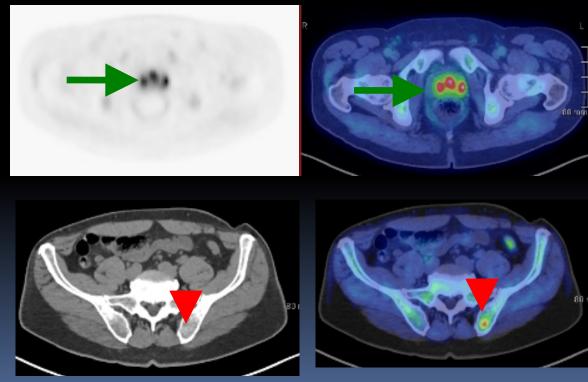


FUTURE DIRECTIONS

STAGING PRIMARY DZ



59 YO S/P WITH HIGH GRADE PROSTATE CANCER ON MULTIPLE BIOPSY SPECIMENS



CONCLUSION

- ❖ In May of 2016, Fluciclovine F-18 was first FDA approved F-18 PET imaging agent for use in patients with suspected recurrent prostate cancer.
- ❖ Shows better accuracy than C-11 choline and In-111 Prostascint, only other radiotracers currently FDA approved for imaging recurrent prostate cancer
- Detection rate increases with increasing PSA
- Familiarization with novel imaging protocol and proper interpretation criteria key to success

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