Incorporating Novel Imaging for Prostate Cancer 2019: Radiation Oncology Perspective

Steven Eric Finkelstein, MD, DABR, FACRO
Florida Cancer Affiliates / The US Oncology Network
Panama City, Florida

Talking Point #1

- PCa imaging is important for proper selections in clinical treatment.

Talking Point #2

- Traditional imaging techniques for metastatic disease (i.e., computed tomography [CT], magnetic resonance imaging [MRI], and radionuclide bone scan) have suboptimal performance in early recurrent or metastatic disease.

Talking Point #3

- Novel positron emission tomography agents including radiolabeled prostate specific membrane antigen (PSMA), choline, and anti-^{18}F-fluorocyclobutane-1-carboxylic acid (^{18}F-FACBC) have demonstrated improved sensitivity and specificity in initial staging and early biochemical recurrence.

Radiologic Techniques for Identification of Prostate Cancer & Metastases – State of Art 2016

Techniques	Use	Sensitivity/Specificity/Issues
TRUS (Transrectal Ultrasound) + Color Doppler	Primary Tool for initial eval of the prostate, surveillance and to guide biopsies	
CT (Computed Tomography)	Staging	Does not give good image of Prostate Small LN may be missed
MRI (Magnetic Resonance Imaging) + Combidex/Feraheme	Zonal anatomy Extracapsular extension Seminal vesicle invasion Improved LN detection	Sensitivity 75% Specificity high PPV ~75% - high FP rate Can have serious reactions
99mTc-MDP Scintigraphy (Technetium Bone scan)	Advanced active osteoblastic activity	Sensitivity 40-94% Specificity 89% Negative results do not rule out bone mets
18F-Sodium Fluoride PET/CT	More subtle osteoblastic activity 3D. Combined with CT for precise anatomic localization	Sensitivity 95% Specificity 95% Much better than Tc-Bone Scan

Radiologic Techniques for Identification of Prostate Cancer & Metastases – State of Art 2016

Techniques	Use	Sensitivity/Specificity
Prostascint (In111 Capromab Pendatide)	Directly detects prostate cancer cells (via intracellular PSMA) Uses older nuclear medicine imaging technique which do not provide good resolution or anatomic precision	Sensitivity 63% PSA > 6 – 10ng/mL Can not see small recurrences/nodes < 1 – 2 cm Long and technically challenging procedure
C11-Choline PET/CT	Imaging lipid membrane synthesis via up-regulation of choline kinase. Identifies local recurrences, small nodes and bone lesions. C11 T1/2 = 20 min	Dependent on PSA level. 74% detection rate, 86% above 2.0ng/mL. Limited value with PSA <2.0ng/mL. Single site use FDA approval [1] Mild urinary excretion
C11-Acetate PET/CT	Imaging lipid membrane synthesis via up-regulation of fatty acid synthase. Identifies local recurrences, small nodes and bone lesions not identified on other imaging. C11 T1/2 = 20 min	Dependent on PSA level. 87% detection rate, 90% above 1.0ng/mL. Performs better than choline at PSA < 3.0ng/mL (77%) [2,3] No urinary excretion

1. Mitchell, C. R., V. J. Lowe, et al. (2013). "Operational characteristics of (11)c-choline positron emission tomography/computerized tomography for prostate cancer with biochemical recurrence after initial treatment." *J Urol* 189(4): 1308-1313.
2. Almeida, F. (2011). PET Imaging Characteristics of C11-Acetate in Patients With Recurrent Prostate Carcinoma. *Arizona Molecular Imaging Center*, NCT01304485
3. Almeida, F., Yen, CK., Finkelstein, S. “Early imaging improves performance of C11-Acetate PET/CT for recurrent prostate adenocarcinoma”. *UroToday International Journal*

Review 2019

Systematic review and meta-analysis	No. of studies	No. of patients	Sensitivity (per lesion) (95% CI)	Specificity (per lesion) (95% CI)	Sensitivity (per patient) (95% CI)	Specificity (per patient) (95% CI)
PSMA						
Perera[10]	N = 16	N = 1309	80% (66-89)	97% (92-99)	86% (37-98)	86% (3-100)
Choline						
Fanti[54]	N = 12	N = 1270			89% (83-93)	89% (73-96)
Evangelista[55]	N = 19	N = 1555	86% (83-88)	93% (90-95)		
Umbehr[56]	N = 12	N = 1055	90% (74-97)	95% (92-97)	85% (79-89)	88% (73-95)
Shen[57] (bone metastases)	N = 9	N = 423	83% (81-85)	95% (94-97)	87% (79-93)	97% (93-99)
Fluciclovine						
Ren[59]	N = 6	N = 251			87% (80-92)	66% (56-75)[a]

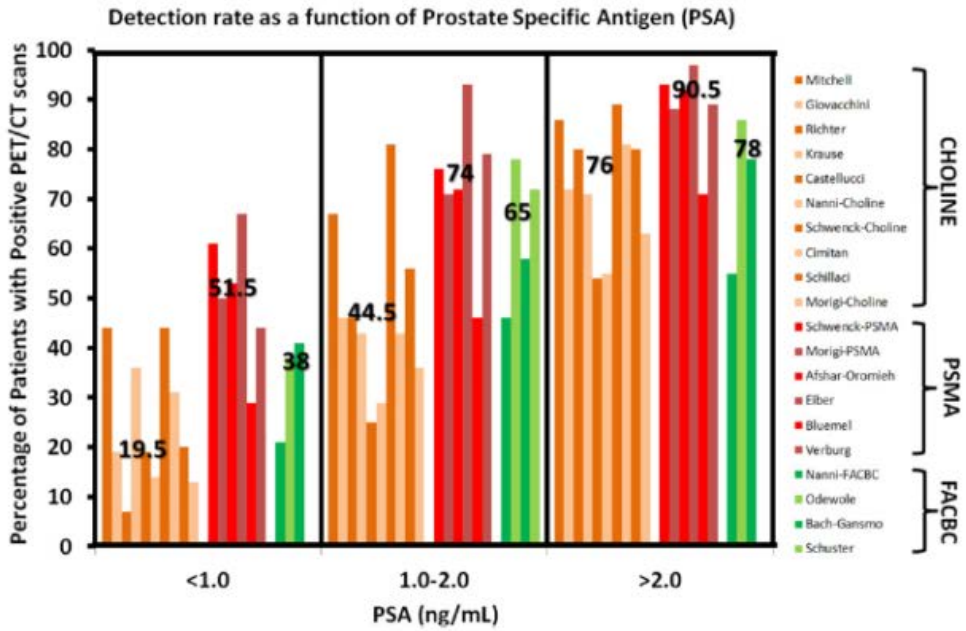
CI, confidence interval; CT, computed tomography; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

[a] Meta-analysis did not include 2 recent studies evaluating operational characteristics for F-18 fluciclovine specificity. Specificity may be higher than reported.

Evans et al. PRO 2019

Review 2019

Study	PET Radiotracer	% of Patients with BCR	% of Patients with Positive PET/CT		
			PSA <1.0	PSA 1.0-2.0	PSA >2.0
Choline					
Mitchell[65]	C-11 Choline	100% (176/176)	44% (15/34)	67% (21/31)	86% (96/111)
Giovacchini[81]	C-11 Choline	100% (358/358)	19% (27/141)	46% (39/85)	72% (95/132)
Richter[82]	C-11 Choline	100% (73/73)	7% (1/15)	46% (6/13)	80% (36/45)
Krause[83]	C-11 Choline	100% (63/63)	36% (8/22)	43% (3/7)	71% (24/34)
Castellucci[84]	C-11 Choline	100% (190/190)	19% (10/51)	25% (10/39)	54% (54/100)
Nanni[66]	C-11 Choline	100% (89/89)	14% (4/28)	29% (8/28)	55% (18/33)
Schwenck[69]	C-11 Choline	100% (101/101)	44% (8/18)	81% (21/26)	89% (51/57)
Cimitan[85]	F-18 Choline	100% (1000/1000)	31% (66/211)	43% (66/153)	81% (513/636)
Schillaci[86]	F-18 Choline	100% (49/49)	20% (2/10)	56% (5/9)	83% (25/30)
Morigi[67]	F-18Methchol	100% (38/38)	13% (2/16)	36% (5/14)	63% (5/8)
PSMA					
Schwenck[69]	Ga-68 PSMA	100% (101/101)	61% (11/18)	76% (20/26)	93% (53/57)
Morigi[67]	Ga-68 PSMA	100% (38/38)	50% (8/16)	71% (10/14)	88% (7/8)
Afshar-Oromieh[87]	Ga-68 PSMA	100% (319/319)	53% (27/51)	72% (28/39)	92% (204/221)
Eiber[88]	Ga-68 PSMA	100% (248/248)	67% (35/52)	93% (67/72)	97% (120/124)
Bluemel[89]	Ga-68 PSMA	100% (32/32)	29% (4/14)	46% (5/11)	71% (5/7)
Verburg[90]	Ga-68 PSMA	100% (155/155)	44% (12/27)	79% (15/19)	89% (97/109)
Fluciclovine					
Nanni[66]	F-18 FACBC	100% (89/89)	21% (6/28)	46% (13/28)	55% (18/33)
Odewole[63]	F-18 FACBC	100% (53/53)	38% (3/8)	78% (7/9)	86% (31/36)
Bach-Gansmo[91]	F-18 FACBC	100% (596/596)	41% (53/128)	58% (N?)	75-85% (N?)
Schuster[62]	F-18 FACBC	100% (93/93)		72% (N?)	



Evans et al. PRO 2019

Multi-Center Multi-Specialty Evaluation of Real World Performance of Novel Fluciclovine F18 PET/CT for Biochemically Recurrent Prostate Adenocarcinoma

Mitchell Finkelstein[1], Jason Efstathiou[2], Jay Beiswanger [3], Christopher Gainer [1], Dennis Healy[3], Warren Hitt[4], Michael Jenkins[3], Saumil Karavadia[5], Edward King[6], Dinesh Rao[6], Richard Roach[6], Andrew Sher[6], Harvey Taub[6], Carlos Ramos[3], Steven Finkelstein[1]

[1]Bay Regional Cancer Center (BRCC), Advanced Urology Institute (AUI), Panama City, Florida, USA. [2]Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA. [3]Advanced Urology Institute (AUI), Panama City, Florida, USA. [4]Advanced Urology Institute (AUI), Panama City, Florida, USA.
[5]Advanced Urology Institute (AUI), Ocala, Florida, USA. [6]Advanced Urology Institute (AUI), Oxford, Florida, USA

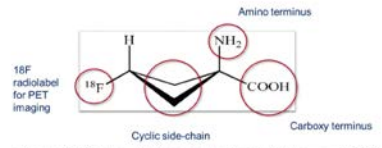
PURPOSE AND BACKGROUND

To evaluate the real world performance of Fluciclovine F18 positron emission tomography/computed tomography (PET/CT) in biochemically recurrent prostate cancer patients.

Evidence of residual recurrent prostate cancer is classically heralded by detectable or increasing serum prostate-specific antigen (PSA), with many patients demonstrating no or minimal evidence of disease on standard imaging studies such as magnetic resonance imaging (MRI), CT, ultrasound, and technetium bone scans.

Subsequent radiation and systemic treatment decisions rely critically on distinguishing between loco-regional relapse in the prostate bed and adjacent soft tissues, locoregional relapse in lymph nodes, and distant metastases.

Axumin (generic name: fluciclovine F18, and previously known as F18 FACBC) is a diagnostic radiopharmaceutical consisting of a synthetic amino acid (an analog of leucine) for PET imaging. Fluciclovine F18 is taken up into prostate tumors by cell surface amino acid transporters which are upregulated in cancer cells.



anti/1-amino-3-18F-fluorocyclobutane-1-carboxylic acid (also known as FACBC)

Figure 1: Molecular structure of Fluciclovine F 18 (Axumin)

PATIENTS & METHODS

Multi-center multi-specialty evaluation of 153 consecutive patients with prostate adenocarcinoma imaged with fluciclovine F18 PET/CT between May 2017 and October 2018.

A dose of 370 MBq (10 mCi) was administered to 153 patients as an intravenous (IV) bolus injection followed by IV saline flush on the PET scanner table, with patient positioned supine with arms above head.

CT scanning for attenuation correction and anatomic correlation was initiated with PET scanning beginning 3 to 5 minutes after completion of injection.

Image acquisition began at mid-thigh to base of skull with total scan time between 20 to 30 minutes.

Target lesions were identified visually and with quantitative measurements of maximal standardized uptake valve (SUV) and lesion-to-background (L/B) ratios obtained for each lesion. Analysis was performed to determine statistical significance.

Analysis was performed to determine statistical significance.

RESULTS

Fluciclovine F18 PET/CT was most commonly (98%, n=150) obtained for rising PSA after prior definitive treatment. In 2% of cases, fluciclovine F18 PET/CT was employed for initial definitive management planning.
Patients with prior initial prostatectomy and prior radiation were similar in number.

Patients with biochemically recurrent prostate cancer had evaluable lesions, which were evaluated across imaging time points. Significant lesions were most commonly detected in lymph nodes, peri-prostate soft tissues, or seminal vesicles (SV).

Lesions involving the lymph nodes, peri-prostate soft tissues, and bone were visu

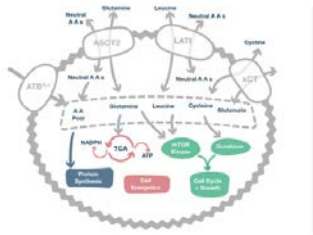
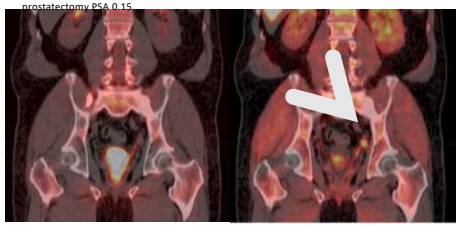


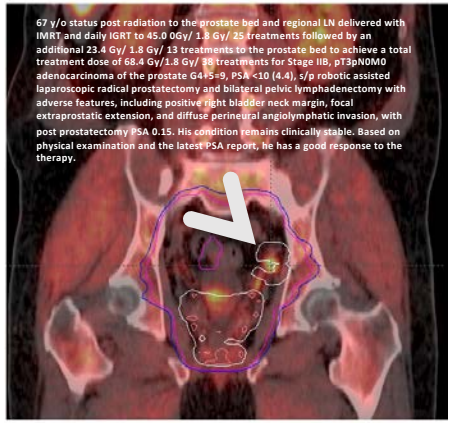
Figure 2: Role of amino acids and their transporters in cellular metabolism

67 y/o with Stage IIB, pT3pN0M0 adenocarcinoma of the prostate G4+5=9, PSA <10 (4.4), s/p robotic assisted laparoscopic radical prostatectomy and bilateral pelvic lymphadenectomy with adverse features, including positive right bladder neck margin, focal extraprostatic extension, and diffuse perineural angiolymphatic invasion, with post prostatectomy PSA 0.15.

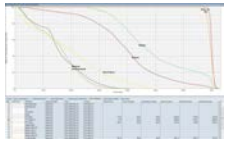


Negative
NA-Fl PET/CT
Bone Scan

Positive Auxmin
Fluciclovine
F18 PET/CT



Treatment Planning CT Fused with Positive Auxmin Fluciclovine F18 PET/CT



CONCLUSIONS

Novel fluciclovine F18 PET/CT appears to aid lesion detection both in terms of maximal SUV and L/B ratios for lesions in real world settings for biochemically recurrent prostate cancer patients.

REFERENCES

1. Axumin (fluciclovine F 18) Injection; US Prescribing Information; Blue Earth Diagnostics, Ltd; August 2016
2. Ganapathy et al., Nutrient transporters in cancer: Relevance to Warburg hypothesis and beyond. Pharmacol & Therap. 2009;121
3. Wang et al. Androgen Receptor and Nutrient Signaling Pathways Coordinate the Demand for Increased Amino Acid Transport during Prostate Cancer Progression. Cancer Research 2011; 71(24), 7525-7536.
4. Oka et al Transport mechanisms of trans-1-amino-3-fluoro[1- 14C] cyclobutanecarboxylic acid in prostate cancer cells Nucl Med Biol 2012;39:109–119
5. Oka et al A Preliminary Study of Anti-1-Amino-3-18FFluorocyclobutyl-1-Carboxylic Acid for the Detection of Prostate Cancer J Nucl Med 2007;48:46–55
6. Oka S, Hattori R, Kurosaki F, Toyama M, Williams LA, Yu W, Votaw JR, Yoshida Y, Goodman MM, Ito O. A preliminary study of anti-1-amino-3-18F-fluorocyclobutyl-1- carboxylic acid for the detection of prostate cancer. J Nucl Med. 2007; 48: 46-55.
7. Okudaira H. et al. Accumulation of Trans-1-Amino-3-[18F]Fluorocyclobutanecarboxylic Acid in Prostate Cancer due to Androgen-Induced Expression of Amino Acid Transporters Mol Imaging Biol. 2014;16:756-64.
8. Schuster et al. Anti-1-Amino-3-18F-fluorocyclobutane-1-Carboxylic Acid: Physiologic Uptake Patterns, Incidental Findings, and Variants That May Simulate Disease. J Nucl Med 2014; 55:1986-92
9. Data on File, Blue Earth Diagnostics, Inc.

Multi-Center Multi-Specialty Evaluation of Real World Performance of Novel Fluciclovine F18 PET/CT for Biochemically Recurrent Prostate Adenocarcinoma

Mitchell Finkelstein[1], Jason Efstathiou[2], Jay Beiswanger [3], Christopher Gainer [1], Dennis Healy[3], Warren Hitt[4], Michael Jenkins[3], Saumil Karavadia[5], Edward King[6], Dinesh Rao[6], Richard Roach[6], Andrew Sher[6], Harvey Taub[6], Carlos Ramos[3], Steven Finkelstein[1]

[1]Bay Regional Cancer Center (BRCC), Advanced Urology Institute (AUI), Panama City, Florida, USA. [2]Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA. [3]Advanced Urology Institute (AUI), Panama City, Florida, USA. [4]Advanced Urology Institute (AUI), Panama City, Florida, USA.
[5]Advanced Urology Institute (AUI), Ocala, Florida, USA. [6]Advanced Urology Institute (AUI), Oxford, Florida, USA

PURPOSE AND BACKGROUND

To evaluate the real world performance of Fluciclovine F18 positron emission tomography/computed tomography (PET/CT) in biochemically recurrent prostate cancer patients.

Evidence of residual recurrent prostate cancer is classically heralded by detectable or increasing serum prostate-specific antigen (PSA), with many patients demonstrating no or minimal evidence of disease on standard imaging studies such as magnetic resonance imaging (MRI), CT, ultrasound, and technetium bone

CT scanning for attenuation correction and anatomic correlation was initiated with PET scanning beginning 3 to 5 minutes after completion of injection.

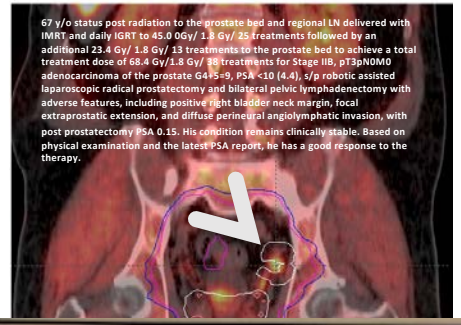
Image acquisition began at mid-thigh to base of skull with total scan time between 20 to 30 minutes.

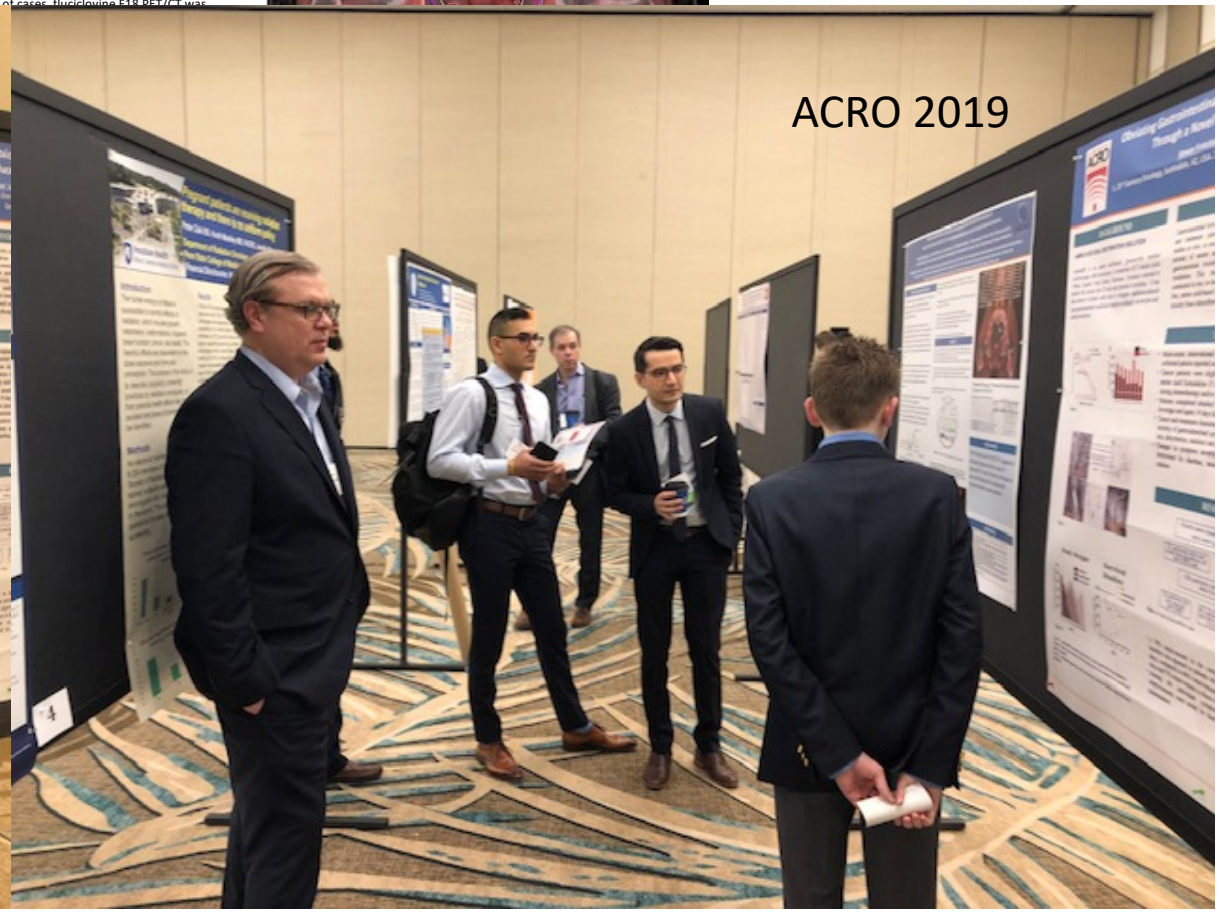
Target lesions were identified visually and with quantitative measurements of maximal standardized uptake valve (SUV) and lesion-to-background (L/B) ratios obtained for each lesion. Analysis was performed to determine statistical significance.

Analysis was performed to determine statistical significance.

RESULTS

Fluciclovine F18 PET/CT was most commonly (98%, n=150) obtained for rising PSA after prior definitive treatment. In 2% of cases, fluciclovine F18 PET/CT was





Discussion Points

- The development of PET tracers in combination with CT and MRI offers superior anatomic localization and biologic correlation of tumor sites, which enhance multi-disciplinary physicians to make appropriate decisions and facilitate treatment.
  - New EBRT/SBRT technology incorporating PET
    - Incorporating ablation of recurrent and oligometastatic disease +/- systemic agents generate abscopal effects
    - Intensifying treatment on PET + dominant nodule
  - Incorporating toxicity mitigating techniques with agents imaged on MRI
  - Incorporating patient experience enhancement

Summary: Potential Consensus Points

- PCa imaging is important for proper selections in clinical treatment.
- Standard conventional imaging for PCa incompletely characterize disease burden.
- Novel positron emission tomography agents including radiolabeled prostate specific membrane antigen (PSMA), choline, and anti-^{18}F-fluorocyclobutane-1-carboxylic acid (^{18}F-FACBC) have improved sensitivity and specificity in initial staging and early biochemical recurrence.
- The development of new PET tracers in combination with CT and MRI offers superior anatomic localization and biologic correlation of tumor sites, which enhance providers' abilities to make appropriate decisions regarding treatment.