Imaging of Prostate Cancer Patients Following Definitive Therapy

Banner MD Anderson Cancer Center

Making Cancer History®

Disclosures

- Bayer

- Janssen

Local vs Metastatic Disease

mpMRI

- Biochemical failure after radical prostatectomy and radiation therapy
- Evaluate for local recurrence vs normal tissue vs scar
- Guide biopsies

Local Recurrence

- 187 men who underwent mpMRI followed by TRUS-guided prostatic fossa biopsy

- Local recurrence was identified in 132 patients, with 124 (94%) detected on e-coil MRI.

- The median PSA was 0.59 ng/mL (range < 0.1-13.1), and median lesion size on MRI was 1 cm.

- Sensitivity, specificity, PPV and NPV was 91%, 45%, 85% and 60% respectively.

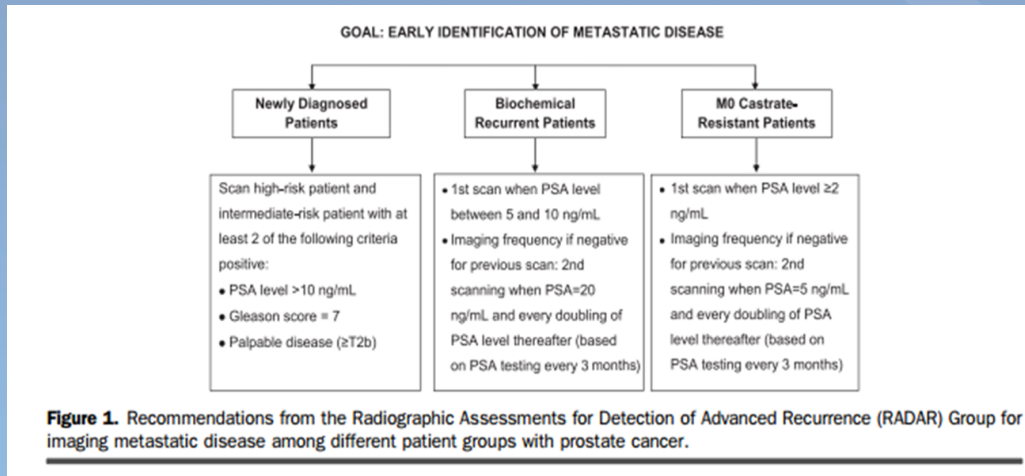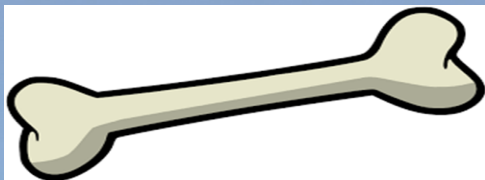Linder BJ, et al. Can J Urol 2014.

mpMRI

- Help targeted biopsies to more accurately diagnose radiation failure and to possibly determine who may benefit more from local or focal salvage therapy.
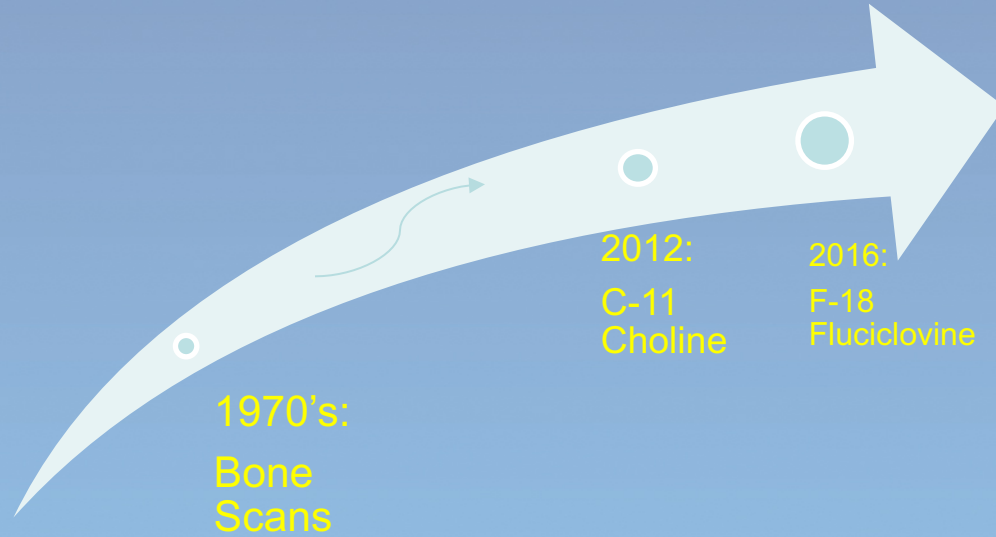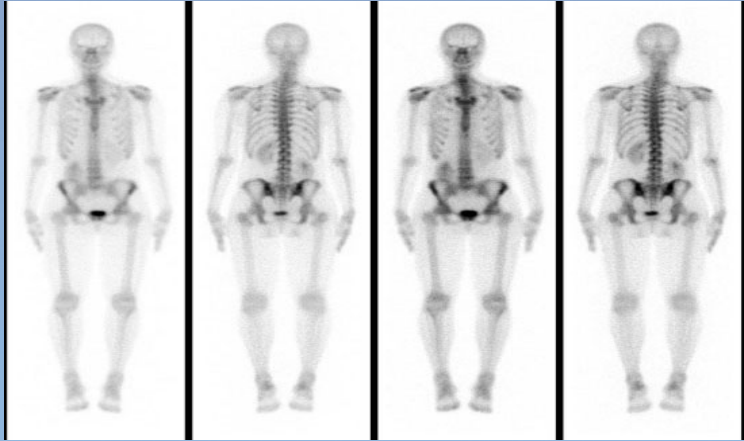
Metastatic Disease

Detection of Metastatic Disease

- RADAR I Recommendations

GOAL: EARLY IDENTIFICATION OF METASTATIC DISEASE

Newly Diagnosed Patients	Biochemical Recurrent Patients	M0 Castrate-Resistant Patients
Scan high-risk patient and intermediate-risk patient with at least 2 of the following criteria positive: • PSA level >10 ng/mL • Gleason score = 7 • Palpable disease (≥T2b)	• 1st scan when PSA level between 5 and 10 ng/mL • Imaging frequency if negative for previous scan: 2nd scanning when PSA=20 ng/mL and every doubling of PSA level thereafter (based on PSA testing every 3 months)	• 1st scan when PSA level ≥2 ng/mL • Imaging frequency if negative for previous scan: 2nd scanning when PSA=5 ng/mL and every doubling of PSA level thereafter (based on PSA testing every 3 months)

Figure 1. Recommendations from the Radiographic Assessments for Detection of Advanced Recurrence (RADAR) Group for imaging metastatic disease among different patient groups with prostate cancer.

Crawford, et al. Urology. March 2014.

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1970's:
Bone Scans

2012:
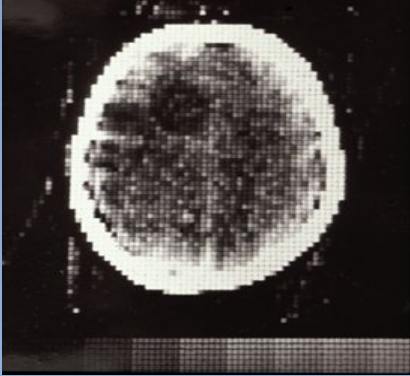C-11 Choline

2016:
F-18 Fluciclovine

Bone Scans

- Early 1970's
- Tc-99m diphosphonates
- Whole body imaging
- Bone only

CT

- 1971
- Soft tissue disease
- Sclerotic and lytic bone metastases
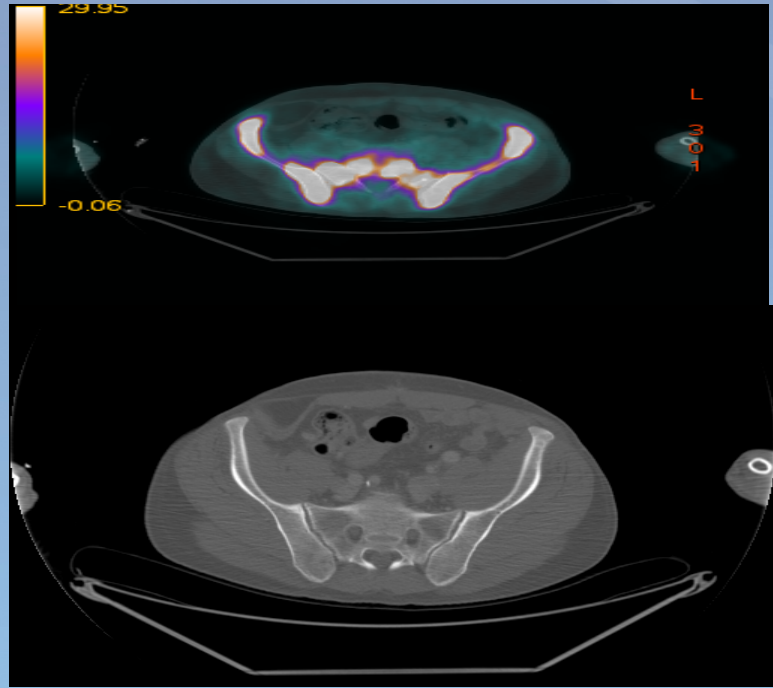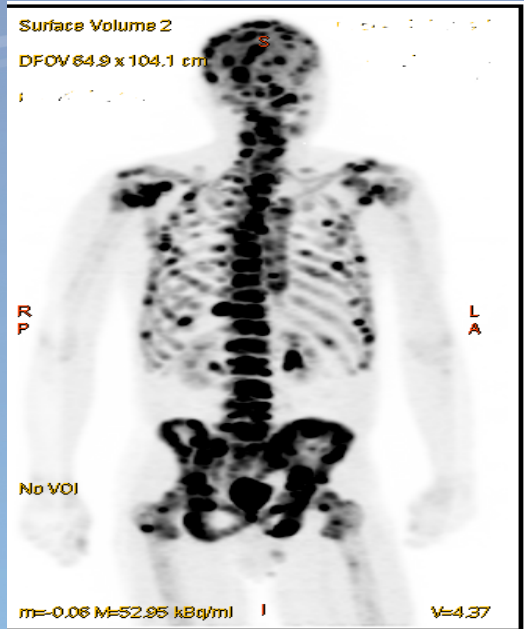
NaF PET/CT

- FDA approved in 1972
- Whole body imaging
- PET/CT
- Bone only

5/18/15
(GS 4 + 5; PSA on 4/9/15: 28.73)

Whole Body MRI

- 1977
- Variable protocols
- Bone only protocols
- Bone and soft tissues?

Prostascint

- 1996
- PSMA
- Bone and soft tissues
- Gamma camera
- Removed from NCCN guidelines

96 HR

FDG
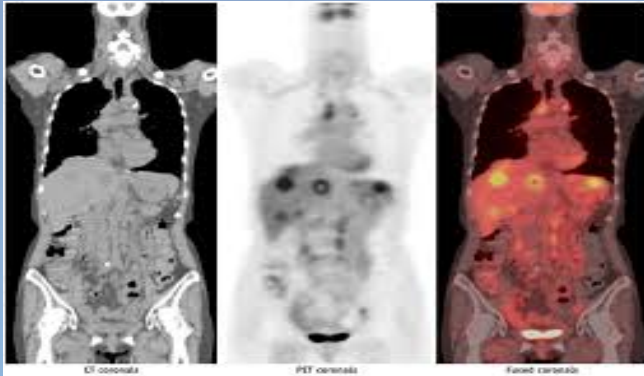
- 1997
- Glucose analogue
- Limited use in prostate cancer
  - Low glucose utilization
  - GU activity
  - Inflammation

C-11 Choline

- FDA 2012
- PET/CT
- Imaging of patients with suspected prostate cancer recurrence and non-informative bone scintigraphy, computerized tomography (CT) or magnetic resonance imaging. In these patients, 11 C-choline PET imaging may help identify potential sites of prostate cancer recurrence for subsequent histologic confirmation. Suspected prostate recurrence is based upon elevated blood prostate specific antigen (PSA) levels following initial therapy.
- NCCN
- Limited availability
    - 20 minute half life

C-11 Choline

Table 2 Diagnostic performance of ^{11}C-choline or ^{18}F-choline PET/CT in the detection of pelvic lymph node metastases in patients with prostate cancer

Diagnostic values	Pooled values (95% CI; $n=609$)	Inconsistency (I^2; %)
Sensitivity	0.59 (0.51–0.66)	78.9
Specificity	0.92 (0.89–0.94)	44.6
Predictive value of a positive test	0.70	
Predictive value of negative test	0.85	
Positive likelihood ratio	6.86 (4.23–11.12)	29.0
Negative likelihood ratio	0.45 (0.28–0.73)	84.4
Diagnostic odds ratio	19.17 (8.39–43.79)	43.8

The table shows pooled data of 11 assessed studies.
CI, confidence interval; CT, computed tomography.

Table 3 Head-to-head studies comparing bone scans and ^{11}C-choline or ^{18}F-choline PET/CT

References	Total number of patients	Number of patients with positive findings		Average interval between tests	Average age (years)	Average PSA (ng/ml)
		Bone scan	Choline PET/CT			
Kwee et al. [64]	30	10	28	NS	70	175
Beauregard et al. [65]	16	2	11	45 days	63	71
Fuccio et al. [66]	25	25	19	NS	70	11
Fuccio et al. [47]	123	0	42	75 days	68	3
Kjolhede et al. [69]	90	0	35	NS	67	28
Picchio et al. [67]	78	19	24	<3 months	69	21
Takesh et al. [68]	18	17	15	14 days	69	5
Total	380	73	174			

CT, computed tomography; PSA, prostate-specific antigen.

C-11 Choline

Table 4 Head-to-head studies comparing PET/CT with ^{18}F-FDG and ^{11}C-choline or ^{18}F-choline as tracers

References	Total number of patients	Number of patients with positive PET/CT		Average interval between tests	Average age (years)	Average PSA (ng/ml)
		^{18}F-FDG	Choline			
Hara *et al.* [6]	10	3	10	NS	78	NS
Price *et al.* [70]	18	13	17	NS	71	364
Picchio *et al.* [71]	100	27	47	5 h	71	7
Garcia *et al.* [72]	38	13	26	Same day	NS	5
Beauregard *et al.* [65]	16	11	11	3 days	63	71
Richter *et al.* [73]	73	22	43	NS	65	5
Watanabe *et al.* [30]	43	8	19	5 h	NS	7
Total	298	99	187			

CT, computed tomography; ^{18}F-FDG, ^{18}F-fluoro-2-deoxy-D-glucose; PSA, prostate-specific antigen.

Limitations

- Availability
  - 20 minute half life

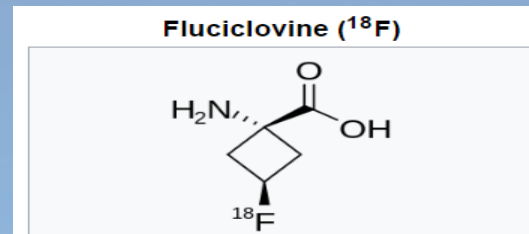 - Limited commercialization/availability
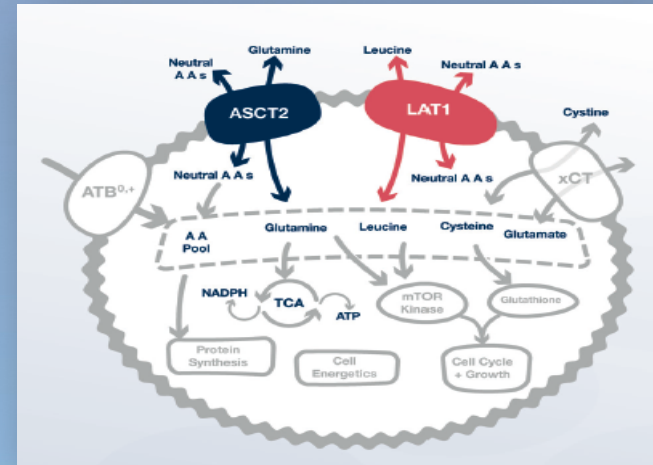
18F-Fluciclovine

- FDA Approved May 2016
- Suspected prostate cancer recurrence based on elevated prostate specific antigen (PSA) levels following prior treatment.
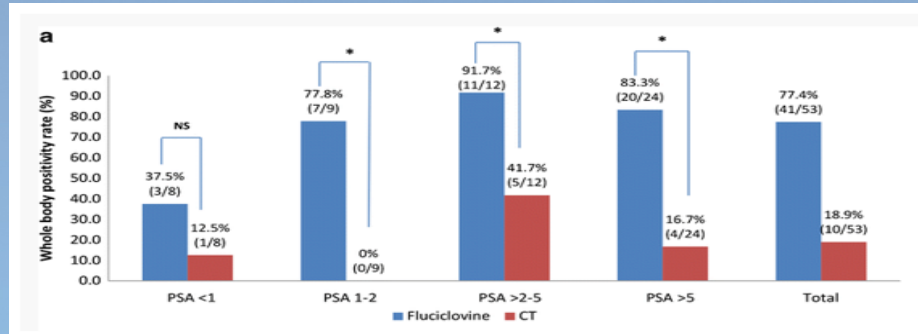

Fluciclovine (^{18}F)

Fluciclovine F18: Mechanism of Action

- Synthetic amino acid that is actively transported into mammalian cells by amino acid transporters (AATs), most notably LAT1 and ASCT2[1,2,3]
  - Not metabolized, nor incorporated into newly synthesized proteins
- Preferentially taken up into prostate cancer compared to surrounding normal tissue
  - Visualization of the prostate/ prostate bed is typically not obscured by bladder activity[4]

1. Oka S, et al. Nuclear Medicine and Biology 2012. 39: 109-119.
2. Okudaira H, et al. J Nucl Med. 2011;52:822-829.
3. Okudaira H, et al. Nuc Med & Biol 2013; 40:670-675.
4. Schuster DM, et al.J Nucl Med 2007. 48:11a-12a.

Fluciclovine vs. CT vs. Prostascint

Agent	Location	Sensitivity	Specificity	Accuracy	PPV	NPV
Fluciclovine F 18 (n=91)	Prostate/ bed	90.2%	40.0%	73.6%	75.3%	66.7%
ProstaScint (n=91)		67.2%	56.7%	63.7%	75.9%	45.9%
Fluciclovine F 18 (n=70)	Extra-prostatic sites	55.0%	96.7%	72.9%	95.7%	61.7%
ProstaScint (n=70)		10.0%	86.7%	42.9%	50.0%	41.9%

Schuster DM, et al. J Urol 2014.
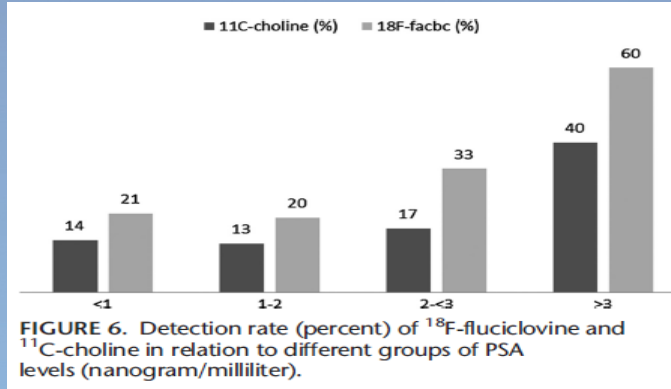
Fluciclovine vs. Choline

- Prospective study with 50 patients
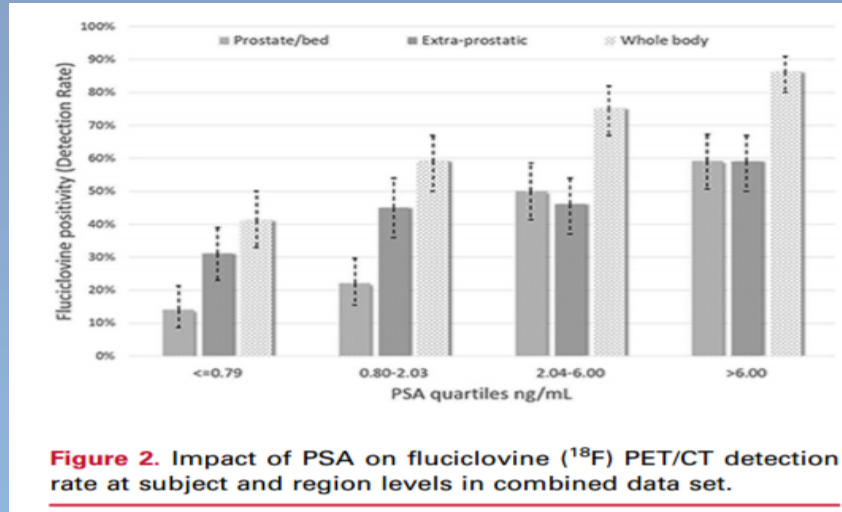
- C-11 Choline and FACBC PET/CT within 1 week

TABLE 2. Patient-Based Analysis

50 Patients	^{11}C-Choline (−)	^{11}C-Choline (+)
Fluciclovine (−)	33	0
Fluciclovine (+)	6	11
	$P < 0.000001$	

TABLE 3. Lesion-Based Analysis

| 17 Fluciclovine-Positive Patients | No. Positive Lesions | |
	^{11}C-Choline (+)	Fluciclovine (+)
6	1	1
1	3	3
1	9	9
2	1	2
1	3	4
3	0	1
2	0	2
1	0	4
	$P < 0.0001$	

Nanni, et al. Clinical Nuclear Medicine. Aug 2015.

FIGURE 6. Detection rate (percent) of ^{18}F-fluciclovine and ^{11}C-choline in relation to different groups of PSA levels (nanogram/milliliter).

Figure 2. Impact of PSA on fluciclovine (^{18}F) PET/CT detection rate at subject and region levels in combined data set.
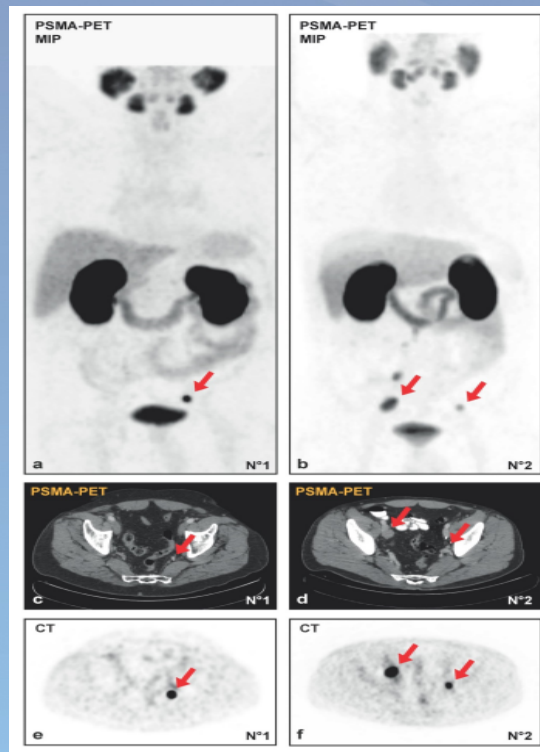
Bach-Gansmo, et al. The Journal of Urology. March 2017.

PSMA PET / CT

- Functional imaging using PET with a radiolabeled PSMA on the surface of prostate cancer cells[1]

- Enables powerful imaging of prostate cancer lesions[1]

- Able to locate the site of biological recurrence even at low PSA levels[1]

- Early clinical studies evaluating the safety and efficacy of Lu-177 PSMA therapy have demonstrated promising results with a significant proportion of men with metastatic prostate cancer[2]

- PSMA- radio guided surgery may improve ability to remove all metastatic nodal tissue[1]

1. Jilg CA et al. *Theranostics*. 2017;7(6):1770-1780.
2. Emmett L et al. *J Med Radiat Sci*. 2017; 64(1): 52–60.

Impact of 18F-Fluciclovine PET on Target Volume Definition for Postprostatectomy Salvage Radiotherapy: Initial Findings from a Randomized Trial

Ashesh B. Jani[1], Eduard Schreibmann[1], Peter J. Rossi[1], Joseph Shelton[1], Karen Godette[1], Peter Nieh[2], Viraj A. Master[2], Omer Kucuk[3], Mark Goodman[4], Raghuveer Halkar[4], Sherrie Cooper[1], Zhengjia Chen[5], and David M. Schuster[4]

[1]Department of Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, Georgia; [2]Department of Urology, Emory University, Atlanta, Georgia; [3]Department of Hematology/Oncology, Emory University, Atlanta, Georgia; [4]Division of Nuclear Medicine and Molecular Imaging, Department of Radiology and Imaging Sciences, Emory University, Atlanta, Georgia; and [5]Department of Biostatistics and Bioinformatics, Emory University, Atlanta, Georgia
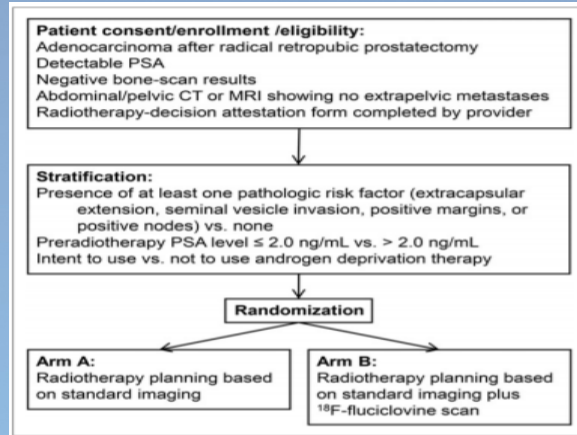
Conclusion: Significant differences in target volume. Higher doses to penile bulb.

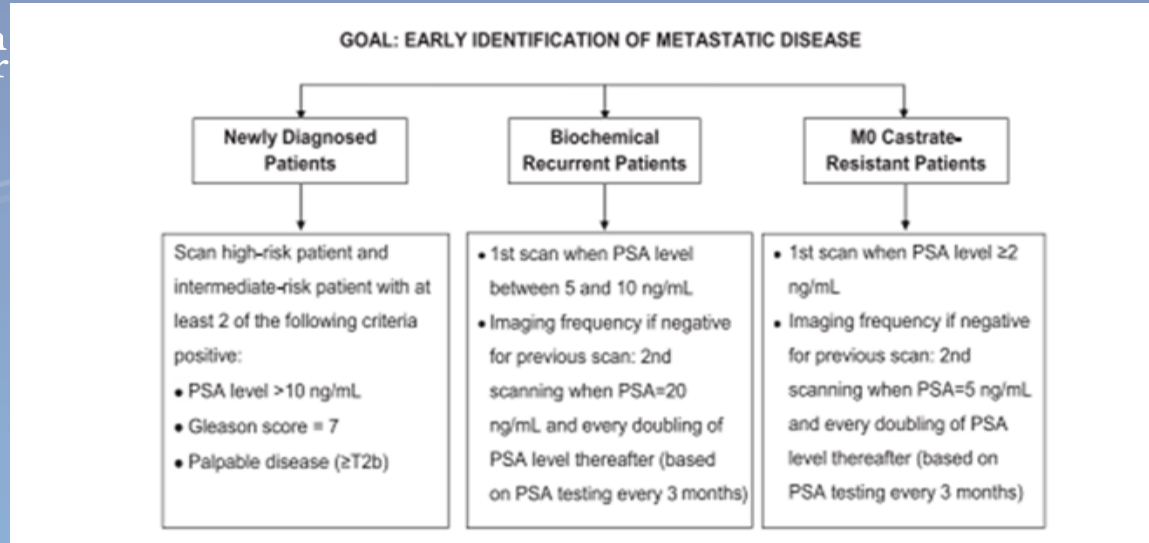# Change in Salvage Radiotherapy

- 87 patients

- 42 randomized to fluciclovine PET/CT

- 34 of 42 had positive findings

- Radiotherapy decisions changed in 17 of 42

  - 2 did not get radiation due extrapelvic disease

  - Radiation field changed in 15

    - 11 prostate bed > prostate bed + pelvis

    - 4 prostate bed + pelvis > prostate bed

Akin-Akintayo, OO, et al. Clinical Nuclear Medicine. January 2017

Change in Management

- Ga-68 PSMA PET
  - 126 patients
  - Major change in management 53%

- F-18 DCFBC PET
  - 68 patients
  - Change in management 51%

Hope TA, et al. JNM. May 2017.
Mena E, et al. EJNMMI. Sep 2017.

Medicare Coverage

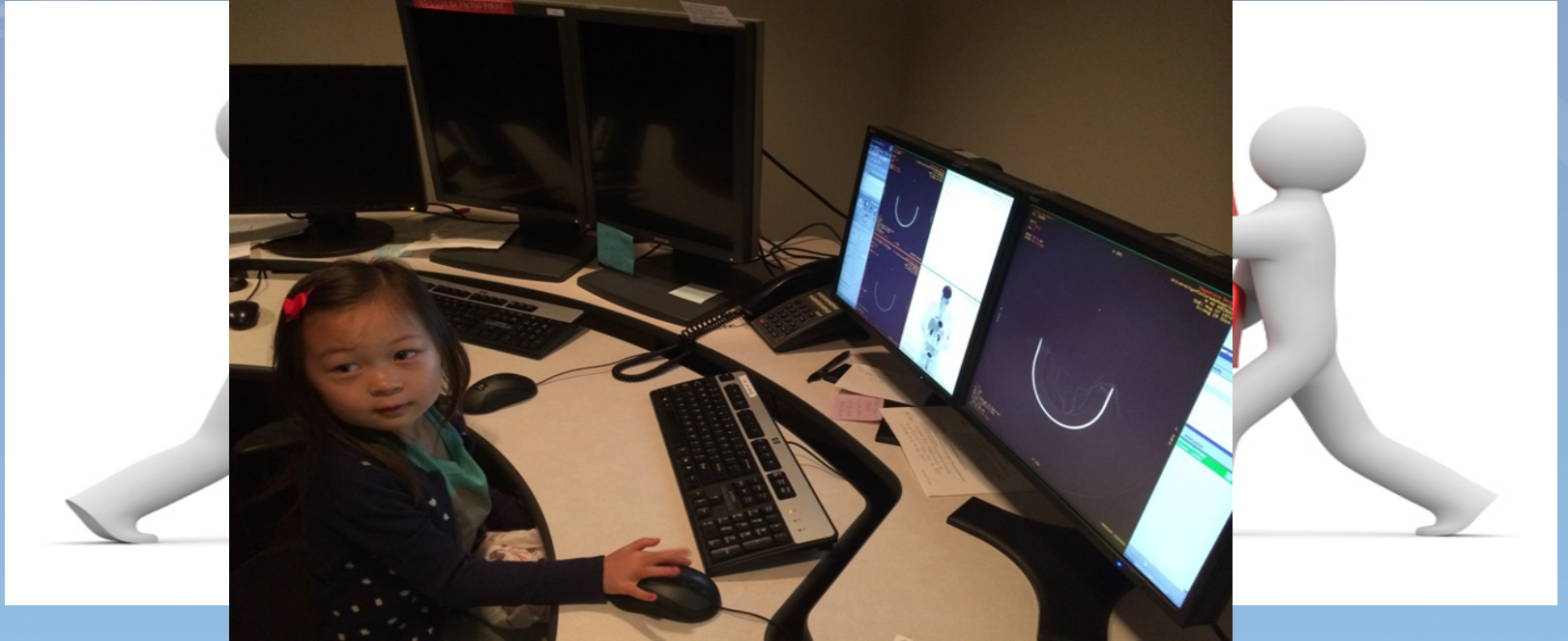| Scan Type	Sites of Disease	Medicare Coverage
Tc-99m Bone Scan	Bone ++ Soft tissue -	Yes
CT	Bone + Soft tissue ++	Yes
Whole Body MRI	Bone +++ Soft tissue ?	No
NaF PET / CT	Bone +++ Soft tissue -	NOPR
FDG PET / CT	Bone +/- Soft tissue +/-	Yes (STS)
C-11 Choline PET / CT	Bone +++ Soft tissue +++	Yes (Limited)
F-18 Fluciclovine PET / CT	Bone +++ Soft tissue +++	Yes
PSMA	Bone++++Soft tissue++++	No

GOAL: EARLY IDENTIFICATION OF METASTATIC DISEASE

Newly Diagnosed Patients

Scan high-risk patient and intermediate-risk patient with at least 2 of the following criteria positive:
- PSA level >10 ng/mL
- Gleason score = 7
- Palpable disease (≥T2b)

Biochemical Recurrent Patients

- 1st scan when PSA level between 5 and 10 ng/mL
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M0 Castrate-Resistant Patients

- 1st scan when PSA level ≥2 ng/mL
- Imaging frequency if negative for previous scan: 2nd scanning when PSA=5 ng/mL and every doubling of PSA level thereafter (based on PSA testing every 3 months)

NaF
PSMA

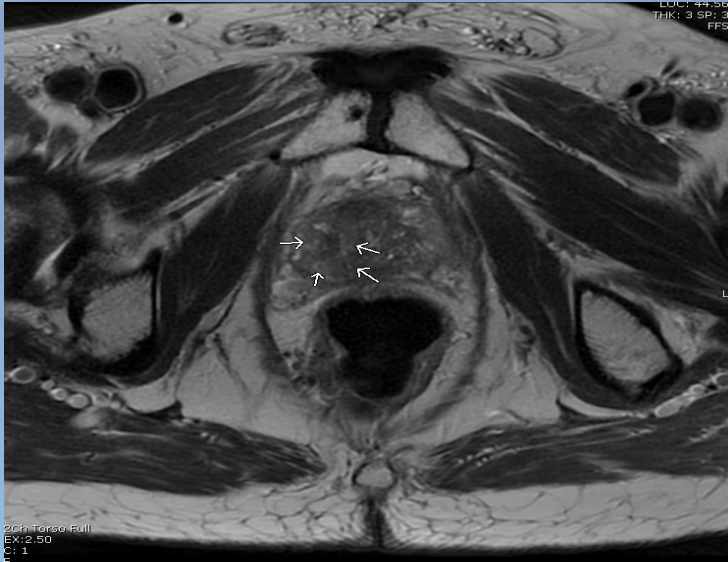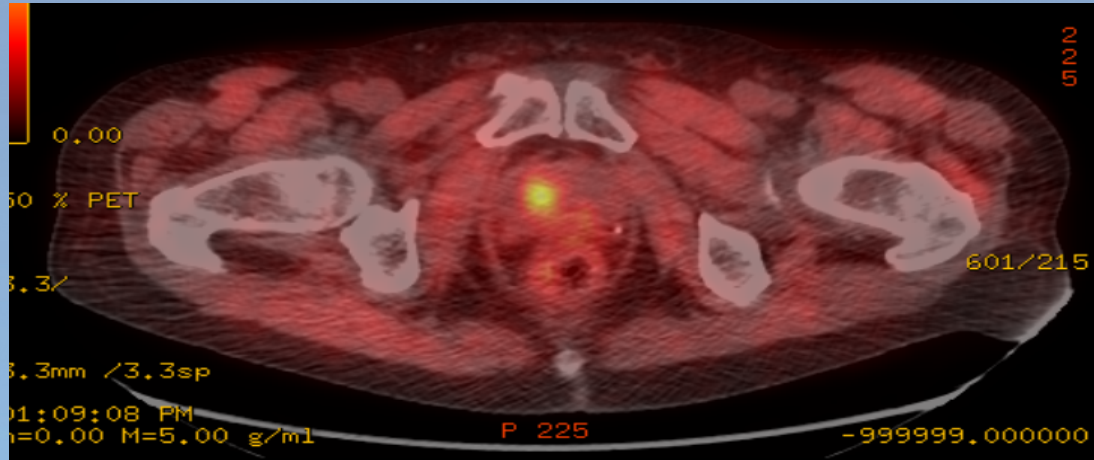Fluciclovine
Choline
NaF
PSMA

FDG

Recommendation

40

Case #1

- 80 year old man
- Gleason 3+3
- Treated with EBRT 2001 (PSA 6.5)

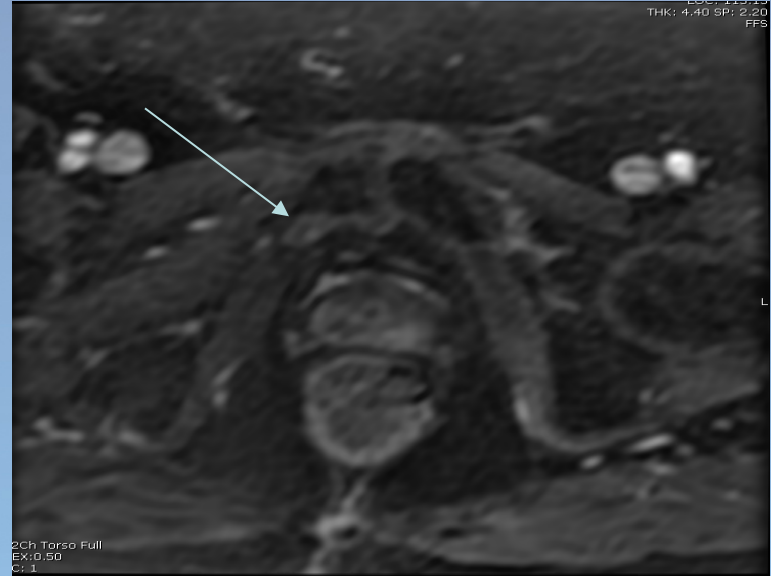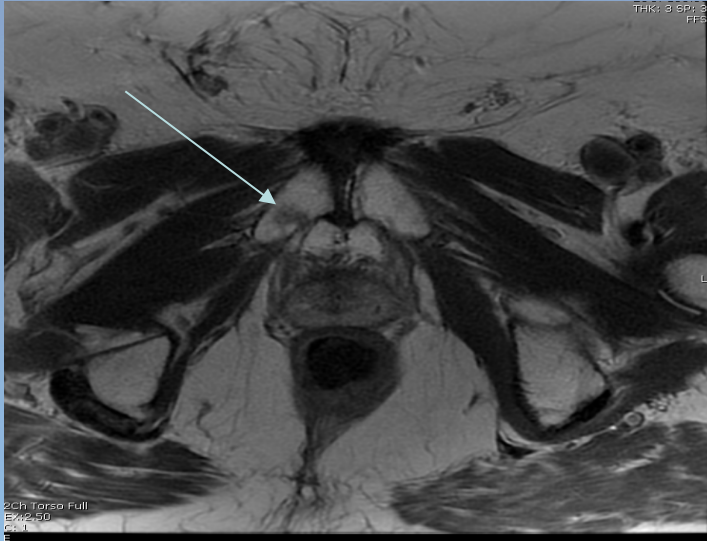- 2/16 PSA 12.2
  - MRI guided bx negative
- PSA 3/28/17 13.4
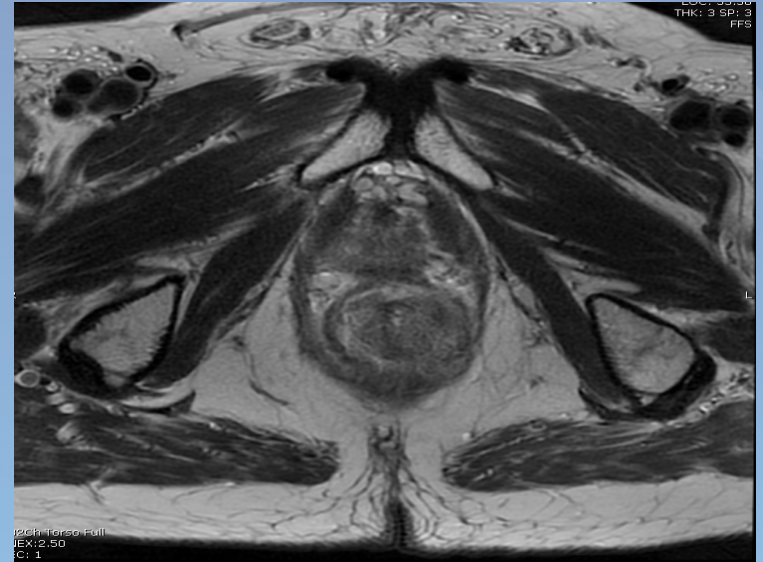
5/1/17: Axumin PET/CT

Case #2

- 74 year old man
- Gleason 3+4
- PSA 6
- EBRT in 2012
- 4/2017 PSA 2.37
- 4/18/17 Bone scan negative