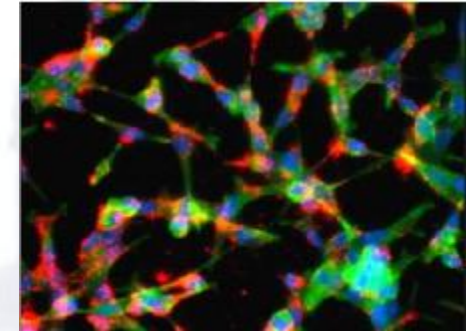
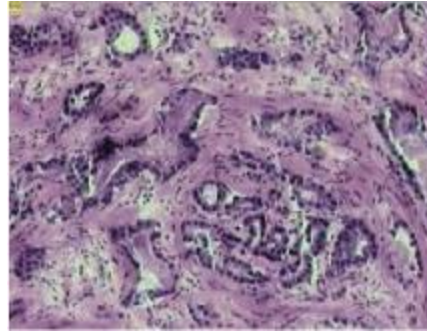
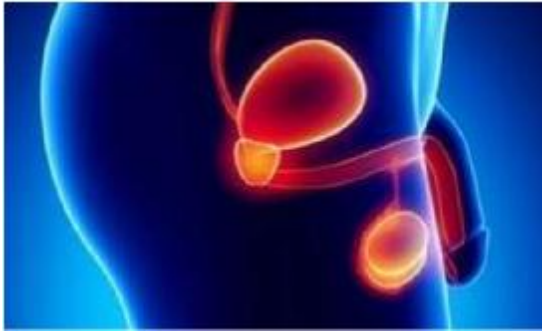


PET-MRI in the Diagnosis and Staging of Prostate Cancer



*2016 Asian-Pacific Conference of Tumor Biology and Medicine
&
The 11th Nanjing Symposium of Molecular Biomarker and Nuclear Medicine Theranostics*

A. Cahid Civelek, M.D.

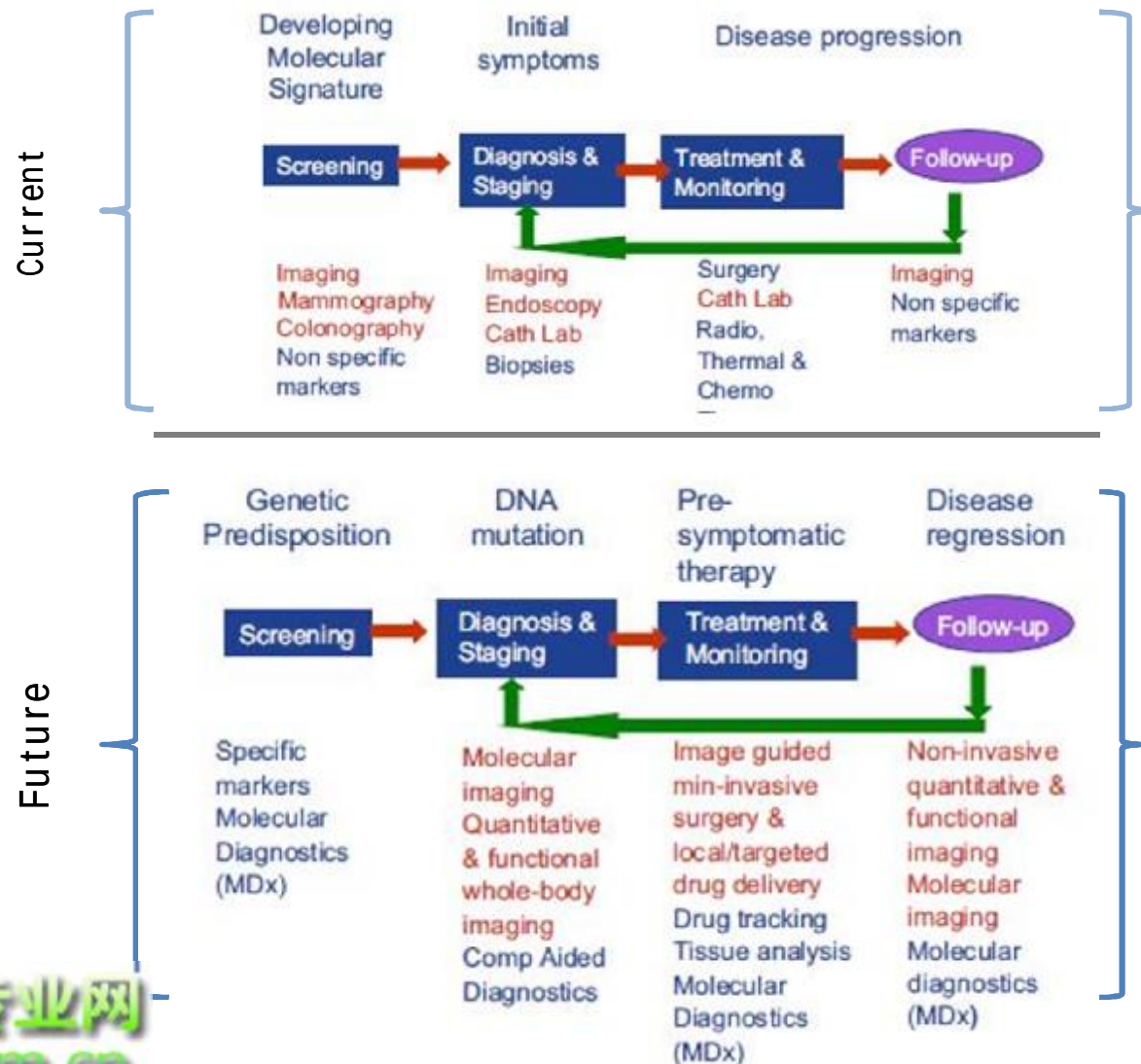
**Department of Radiology and Imaging Sciences
Bethesda, Maryland, USA**

OUTLINE

I will briefly review the

- Existing treatment and diagnostic challenges that we face in the management of patients with prostate cancer,
- Recent potential clinical improvements and changes taking in place, and then talk about
- How we the field of Nuclear Medicine fit in this New Era with our new agents, and technologies, including the MRI-PET.

Current and Future role of imaging in cancer management



Identification of a strong predictor of which men with prostate cancer will develop resistance to androgen deprivation therapy (ADT) would be great

Researchers Identified Genetic Mutation Associated With Poor Outcomes in Prostate Cancer.

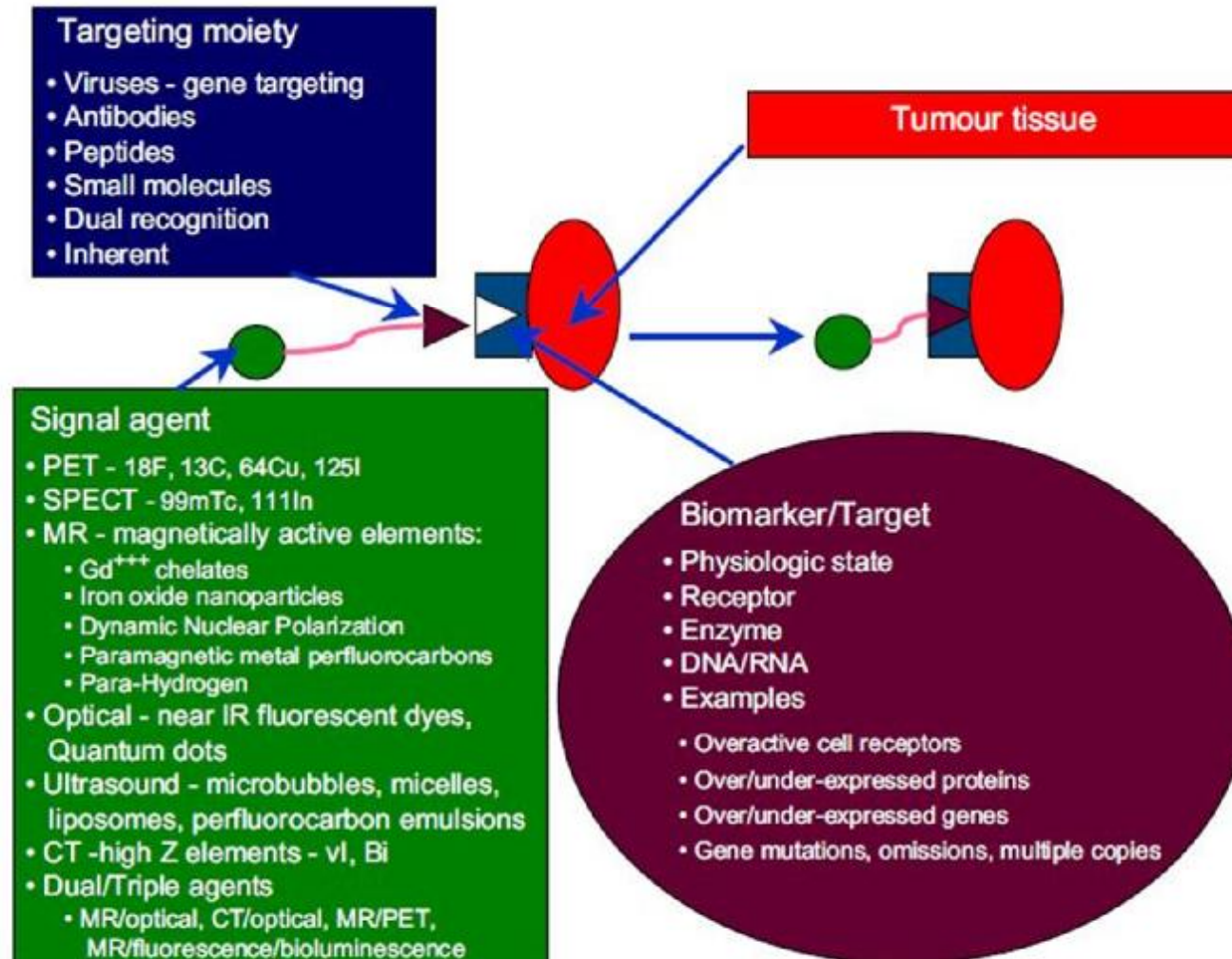
Investigators reported in The Lancet Oncology that inheritance of the HSD3B1 (1245C) allele that enhances dihydrotestosterone synthesis appears to be associated with prostate cancer resistance to ADT.

Theory: HSD3B1 could potentially be a powerful genetic biomarker capable of distinguishing which men may need less aggressive therapy from those whose warrant early escalated therapy.

Would be Outcome: A simple blood test to detect the presence of the polymorphism, personalizing prostate cancer treatment.

A simple blood test could allow us to personalize therapy by telling us which patients need to be treated more aggressively, such as with more intensive hormonal therapy, On the contrary, patients with metastatic cancer who do not carry the polymorphism may fare better with ADT alone.

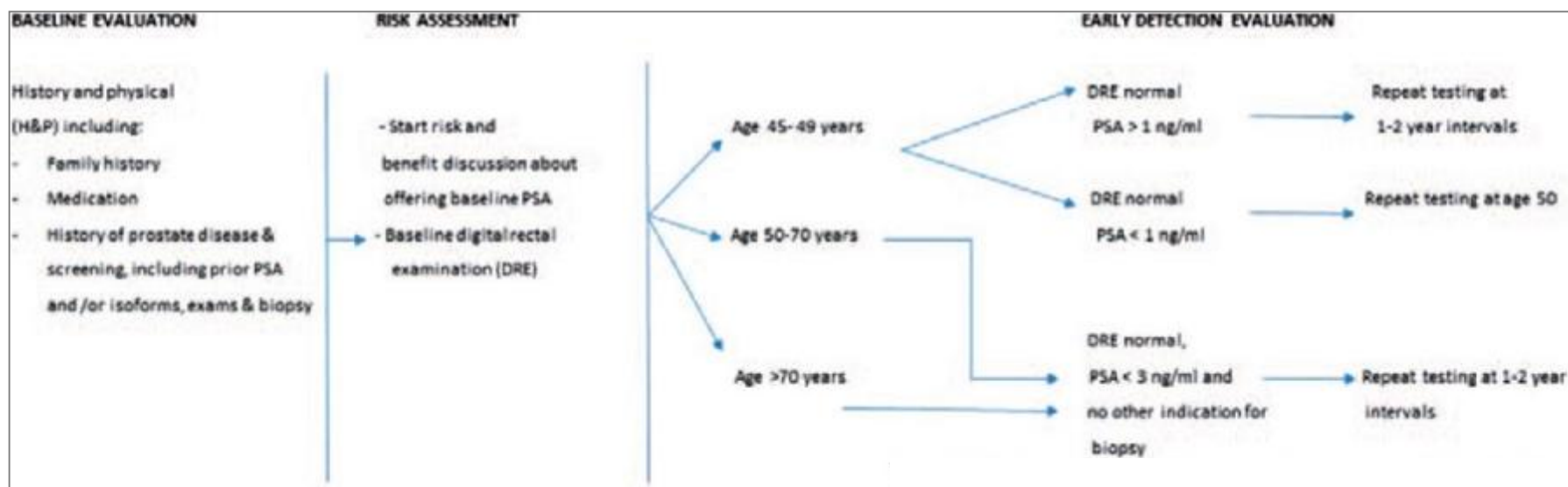
Biomarker Imaging



Clinical Perspective

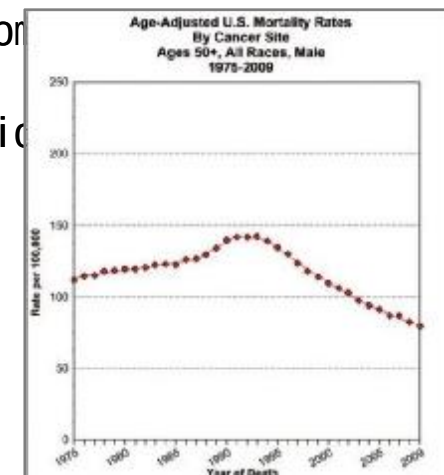
Prostate Cancer

Screening for prostate cancer algorithm



In 2013, an estimated 238,590 new cases of prostate cancer and 29,720 deaths occurred, making it the second leading cause of cancer death in US men

- Widespread prostate cancer screening with prostate-specific antigen (PSA) has led to a dramatic reduction in the proportion of men diagnosed with metastatic disease and prostate cancer death rates
- However, PSA screening continues to be highly controversial due to its limited specificity for clinically significant prostate cancer, resulting in unnecessary biopsies for false positive results as well as detection of some indolent tumors that would not have caused harm during the patient's lifetime.
- Routine use of PSA screening and DRE are no longer recommended
- To preserve the benefits of screening and early detection and to reduce these harms, there has been great progress into alternate ways of using the PSA test with better performance characteristics



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- In the early 1990s, several studies showed that a greater percentage of PSA circulating in the unbound or form (‘free PSA’) indicated a greater likelihood that the elevation was from benign conditions rather than prostate cancer
 - More recently, several PSA isoforms have been identified that can further increase the specificity for prostate cancer. In particular, the [-2] form of proPSA (‘p2PSA’) has become commercially available, with improved performance over either total or free PSA for prostate cancer detection on biopsy.
 - The Prostate Health Index (PHI) is a new formula that combines all three forms (total PSA, free PSA and p2PSA) into a single score that can be used to aid in clinical decision-making.
 - PHI also predicts the likelihood of progression during active surveillance, providing another noninvasive modality to potentially select and monitor this patient population.
 - This new blood test provides significant promise for both prostate cancer screening and treatment decision-making.

Prostate Health Index (PHI)

Prostate Health Index (PHI) is a combination of 3 different isoforms of PSA, that is:

total PSA,
free PSA (fPSA), and
pro-PSA,

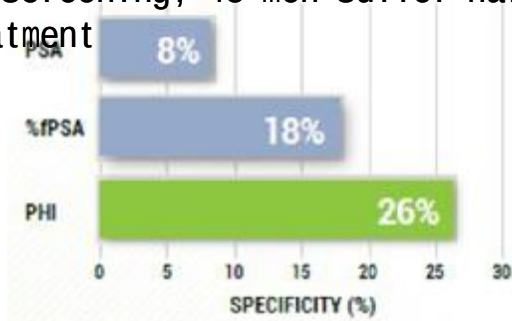
X

PHI is also consistently associated with Gleason score and upgrading during active surveillance.

PHI should be considered as part of the standard urologic armamentarium for biopsy decisions, risk stratification and treatment selection

Prostate Health Index (PHI)

- Over 1 million US men per year have prostate biopsies due to elevated PSA, but only 25% actually have cancer.
- Biopsies can have complications such as fever, infection, bleeding, urinary problems, and pain.
- It is currently difficult to distinguish prostate tumors that are destined to be lethal (~15%) from those that will remain indolent and non-life threatening (~85%).
- As a result, overtreatment often occurs, which can lead to erectile dysfunction, urinary or bowel incontinence, and serious surgical complications.
- It is estimated that for every life saved by PSA screening, 48 men suffer harm from treatment



Current problem: Therapy Associated Poor Outcomes in Prostate Cancer ^{1/4}

After definitive local treatment, **Gonadal suppression**, achieved by surgical or pharmacological castration, is a mainstay of therapy for recurrent prostate cancer and metastatic disease.

Most men initially respond favorably to gonadal suppression, however, virtually all eventually develop biochemical or clinical evidence of disease progression after around

- 2 – 10 years in the non-metastatic setting and
- 1 – 3 years in the metastatic setting.

This clinical state, known as **castration-resistant prostate cancer**, is usually heralded by a shift in androgen signaling from gonadal androgens to adrenal and intra-tumoral androgens.

However, the reasons for this variability in the duration of response to primary gonadal suppression are poorly understood.

Identification of a strong predictor of which men with prostate cancer will develop resistance to androgen deprivation therapy (ADT) would be great

Researchers Identified Genetic Mutation Associated With Poor Outcomes in Prostate Cancer.

Investigators reported in The Lancet Oncology that inheritance of the HSD3B1 (1245C) allele that enhances dihydrotestosterone synthesis appears to be associated with prostate cancer resistance to ADT.

Theory: HSD3B1 could potentially be a powerful genetic biomarker capable of distinguishing which men may need less aggressive therapy from those whose warrant early escalated therapy.

Would be Outcome: A simple blood test to detect the presence of the polymorphism, personalizing prostate cancer treatment.

A simple blood test could allow us to personalize therapy by telling us which patients need to be treated more aggressively, such as with more intensive hormonal therapy, On the contrary, patients with metastatic cancer who do not carry the polymorphism may fare better with ADT alone.

What implications do these findings have for clinical practice?

If these data can be analytically and clinically validated, HSD3B1 (1245C) could be used as a prognostic indicator of clinical benefit to gonadal suppression therapies and could be obtained easily from a germline DNA sample.

The greatest relevance of this biomarker would be in selection of those patients who might benefit from early escalated therapy.

It is therefore tempting to speculate that men with the HSD3B1 (1245C) genotype might derive the greatest benefit from a combination of gonadal suppression plus concurrent docetaxel chemotherapy. Alternatively, these patients might need a combination of the early use of gonadal suppression plus a novel hormonal therapy, such as enzalutamide or abiraterone.

Abiraterone is a selective, potent CYP17A1 inhibitor that decreases extra-gonadal androgen synthesis and can improve survival in men with metastatic castration-resistant prostate cancer.

Germline and somatic biomarker information can and should be used in the future to help direct therapy in men with recurrent and advanced prostate cancer.

Determinants of long-term survival of patients with locally advanced prostate cancer: the role of extensive pelvic lymph node dissection

A retrospective analysis of data from 1586 [pT3-T4] PCa patients treated with RP and extended PLND between 1987 and 2012

- Average number of nodes removed was 19. Mean follow-up was 80 months.
- At multivariable analyses, Gleason score 8-10 (HR 2.5) and a higher number of positive nodes (HR 1.06) were independently associated with higher CSM rate (all $P < .05$).
- Higher number of removed LNs (HR 0.94) and adjuvant radiotherapy (HR 0.54) were independent predictors of lower CSM rates (all $P \leq .03$).

In pT3-T4 prostate cancer (PCa) patients, RLNs were directly and positively related to cancer-specific mortality (CSM).

Removal of a higher number of lymph nodes (LNs) during radical prostatectomy (RP) was associated with higher CSM.

Higher number of removed LNs and Adjuvant Radiotherapy was associated with lower CSM rates.

First study to examine the effect of extended pelvic lymph node dissection (PLND) on cancer survival in pT3-pT4 prostate cancer.

Extended PLND should be considered in patients with significant pre-operative risk of harboring adverse pathological stage.

Prostate cancer survival benefit with extended pelvic lymph node dissection

Adjuvant radiation therapy is associated with better oncological outcome compared to salvage radiation therapy in patients with pN1 prostate cancer treated with radical prostatectomy.

A total of 773 patients with LN positive prostate cancer (PCa) at RP with or without additional radiation treatment from 2005 to 2013 were retrospectively analyzed.

- 505 patients received no treatment after RP or sRT at BCR (NT/sRT), 213 received aRT and 55 received aHT only.
- Overall 4 y BCR- and metastasis-free survival rates were 43.3% and 86.6%, respectively.
- aHT and NT/sRT were independent risk factors for BCR (HR, 2.14; P=.002 and HR, 2.22; P<.001) and metastasis (HR, 2.81; P=.014 and HR, 2.78; P<.001) compared to aRT.
- 4 y BCR-free survival was 43.0% with NT/sRT vs 57.5% with aRT (P<.001).
- 4 y metastasis-free survival was 82.5% and 91.8%, respectively (P=.021).
- Risk for metastasis was significantly higher with late sRT (pre-RT prostate-specific antigen >0.5 ng/mL) vs early sRT (HR, 2.24; P=.023).
- Two-thirds of patients with LN-positive PC at RP show biochemical recurrence (BCR) within 5- year and more than one-third develop metastases within 10-year.
- Lymph node (LN)-positive prostate cancer (PC) patients at radical prostatectomy (RP), who received adjuvant radiation (aRT) had a significantly better oncological outcome compared to patients with NT/sRT independent of tumor characteristics. Patients with early sRT showed higher rates of response and better metastasis-free survival than patients with pre-RT PSA >0.5 ng/ml.

The changing Role of the Radiologist & Nuclear Medicine Physician in the management of Advanced Prostate Cancer Patients

Diagnostic Tests: PET- CT & PET- MRI:

- ^{18}F -fluciclovine (Axumin)* [^{18}F -ACBC]
- Choline Based tracers:
 - ^{18}F -fluoroethylcholine (FECH)
 - ^{18}F -methycholine
 - ^{11}C -choline
- ^{18}F -DCFPyL PSMA Hopkins agent
- ^{68}Ga -PSMA*

Therapeutic Agents:

^{223}Ra dicloride (Xofigo)*

Administered in a longitudinal fashion over 20 weeks rather than a single visit.

*FDA approved

Castration Resistant Prostate cancer



Super Scan

Bone Matrix - Calcification imaging

(^{18}F -NaF)

^{18}F -NaF PET-CT is a well-established and validated qualitative and quantitative skeletal imaging tool.

^{18}NaF undergoes chemisorption into bone crystals and exchanges rapidly with OH on the surface of the hydroxyapatite matrix ($\text{Ca}_{10}(\text{PO}_4)_6\text{OH}_2$) to form fluoroapatite ($\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$). ^{18}F -NaF uptake and retention in bone depends on blood flow and osteoblastic activity and has been used in a variety of benign and malignant bone disorders.

^{18}F -NaF PET-CT shows higher sensitivity and specificity compared to the more commonly used bone scintigraphic methods performed on a γ -camera for detection of osseous metastases in men with prostate cancer. The clinical use of ^{18}F -NaF PET-CT is expected to grow on the basis of increasing availability of PET-CT scanners and the lingering uncertainty on the supply of $^{99\text{m}}\text{Tc}$ -labeled compounds.

The use of ^{18}F -NaF PET-CT has also been investigated in animals and in patients to assess micro-deposition of calcium in atherosclerotic plaques. It was found that ^{18}F -NaF activity correlates with high risk coronary plaque features and is a promising approach for the evaluation of active calcification and identification of the vulnerable atherosclerotic plaque.

Planar versus SPECT-CT Bone scan



Facts

After radical prostatectomy or radiation therapy, Biochemical recurrence has been reported in 27% – 53% of patients.

Radiology and Nuclear Medicine Imaging techniques play an important role in the detection of local relapse and lymph node and skeletal metastases.

Most institutes rely on ‘multi-parametric MRI’ technique for this purpose. The main advantage of MRI is its excellent anatomic resolution - highly accurate in detecting local recurrence.

PET/CT has advantage due to its ability to demonstrate biochemical or physiological phenomena, thus, facilitating differentiation between benign and malignant lesions.

PET/MRI combining advantages of the PET and MRI modalities, may be even be more beneficial.

PET/MRI matches PET/CT for recurrent pelvic cancer

PET/MRI may offer accurate assessment of cancer patients by combining simultaneous whole-body PET with whole-body MRI. MRI's benefits include:

Excellent soft-tissue contrast and significantly higher lesion contrast and diagnostic confidence in the detection of malignant lesions compared to MRI alone.*

Markedly reduced radiation exposure compared to full-dose FDG-PET/CT. (particular importance considering repetitive examinations for follow-up imaging of cancer patients, especially for a younger patient population and/or tumor entities that are associated to low mortality rates).

However, PET/MRI does suffer from longer scan time due to the need for additional MRI sequences.

Hence, well-considered and suitable MR imaging protocols are required.

Use a first post-contrast subtracted, or FAST, imaging protocol, which consisted of:
a whole-body diffusion-weighted echo-planar imaging (EPI) sequence,
a half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequence, and
a post-contrast 3D volumetric interpolated breath-hold examination (VIBE) sequence.

The results suggest that PET/MRI with FAST could be a viable alternative for the diagnostic workup of patients with pelvic and gynecological cancer.

MRI Protocol for Staging Newly Diagnosed Prostate Cancers

“One-Stop-Shopping”

A recent article in the American Journal of Radiology reports that a multiparametric MRI of the

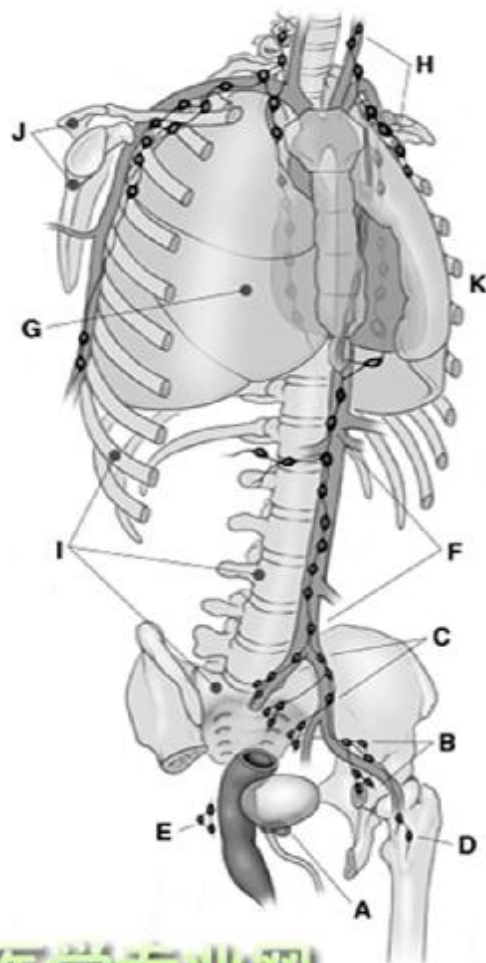
- prostate and pelvis combined with an MRI of the
- lumbar spine

serves well as a single staging study for high-risk intermediate and high-risk prostate cancer.

This one study (multiparametric MRI) can replace the current customary CT of the pelvis often in conjunction with a ^{99m}Tc -MDP or ^{18}F -NaF PET/CT imaging of the skeletal system.

Radiologically identified Relapse sites of CaP

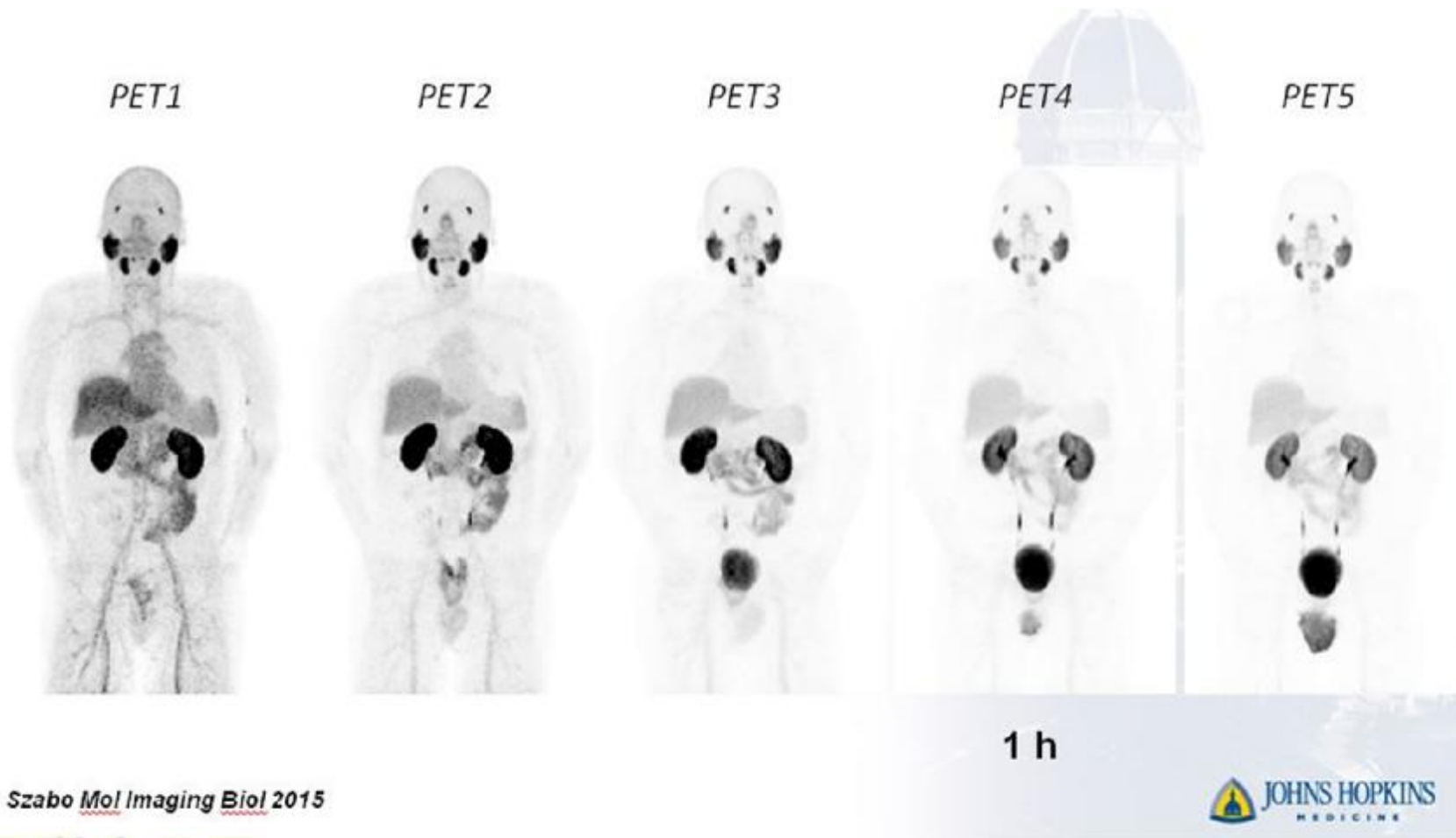
(n= 202 men)



A. Local Disease	102 (50.4%)
B. Pelvic LN distal to common iliac bifurcation	74 (36.6%)
C. Pelvic LN distal to aortic bifurcation	43 (21%)
D. Inguinal LN	2 (0.99%)
E. Perirectal	18 (8.9%)
F. Retroperitoneal LN	21 (10.3%)
G. Chest	8 (3.9%)
H. Neck	8 (3.9%)
I. Axial Bone	26 (12.8%)
J. Appendicular Bone	17 (8.4%)
K. Miscellaneous	2 (0.99%)

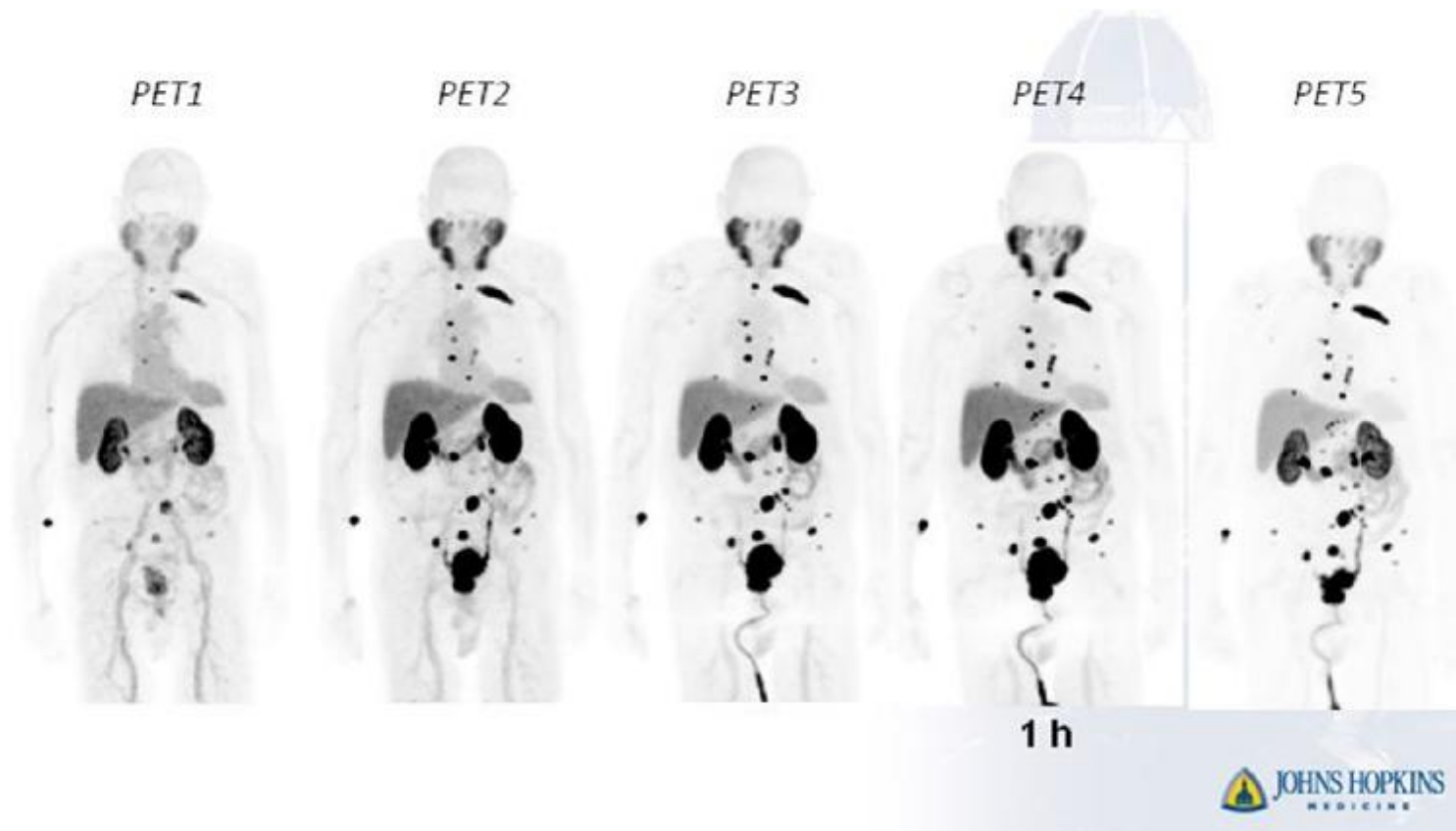
Normal human biodistribution

Second generation: ^{18}F -DCFPyL

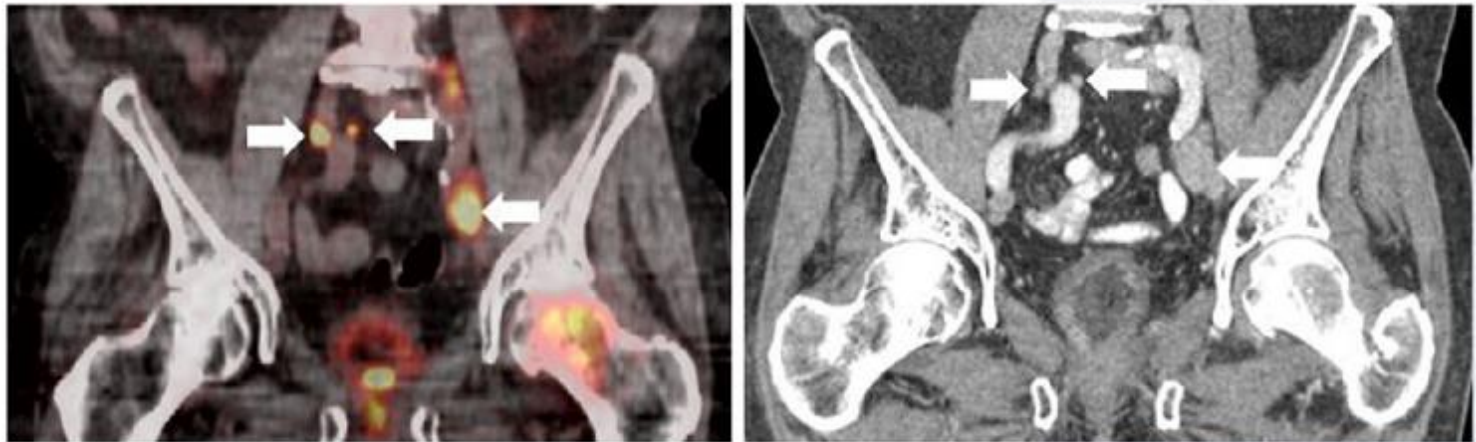


Second generation: ^{18}F -DCFPyL

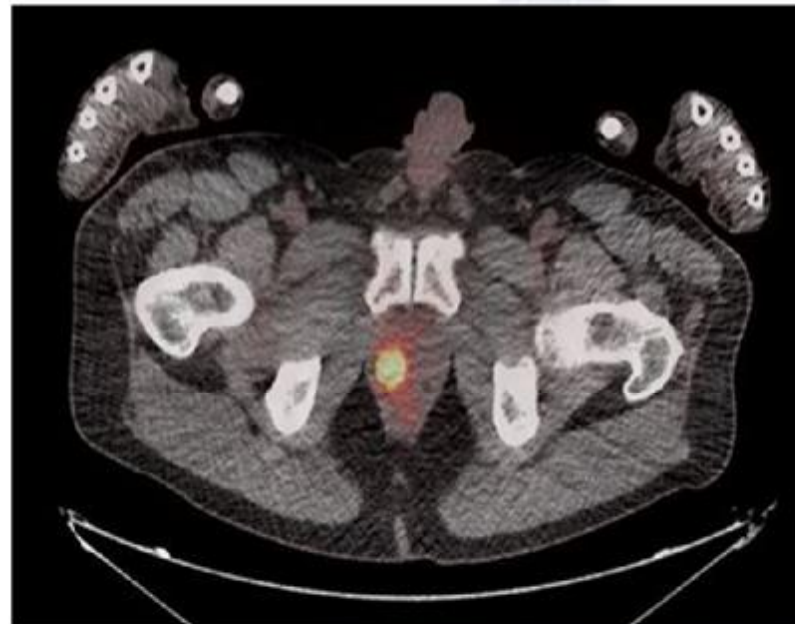
Metastatic castration-resistant prostate cancer



^{18}F -DCFPyL identifies lymph node metastases



^{18}F -DCFPyL identifies intra-prostatic disease in high risk patients

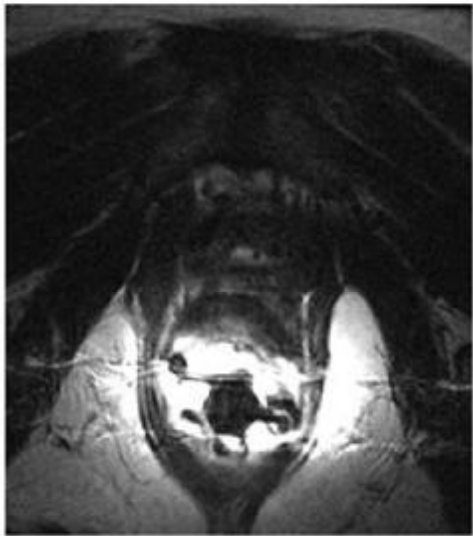


cT2a, PSA = 11.9, Gleason 4 + 4 = 8 on biopsy in two cores in the right mid and lateral apex; SUV = 38.5

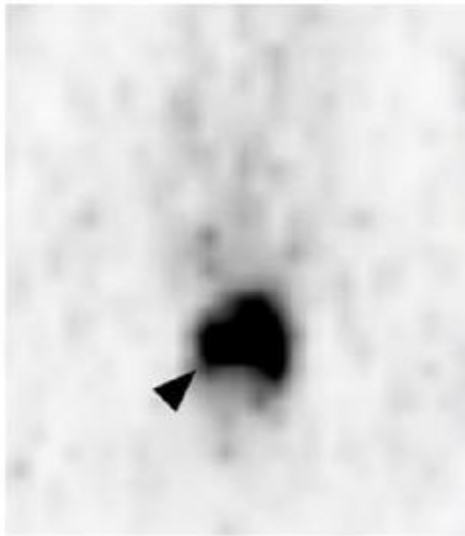


Rectal wall recurrence, occult on MR with endorectal probe

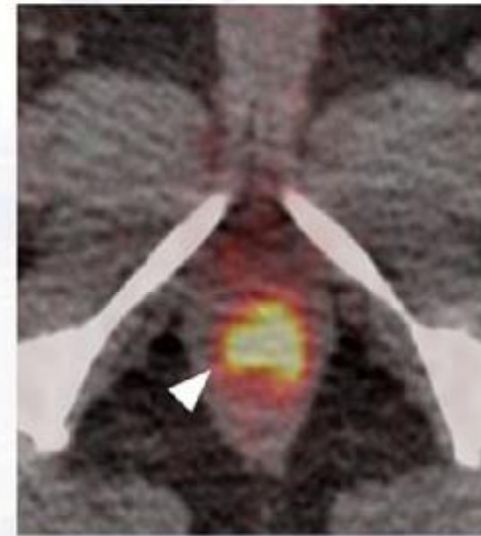
Axial T2W MR



Axial ^{18}F -DCFPyL PET

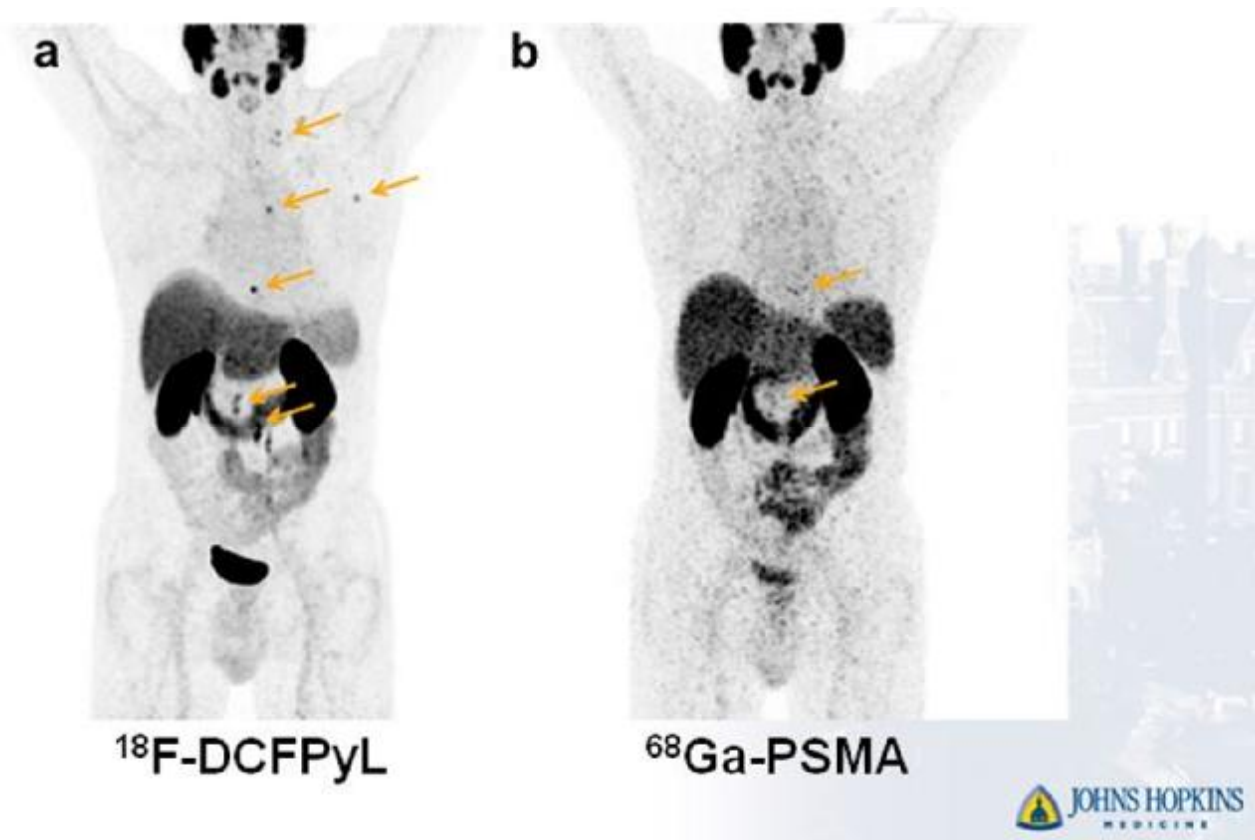


Axial ^{18}F -DCFPyL PET/CT

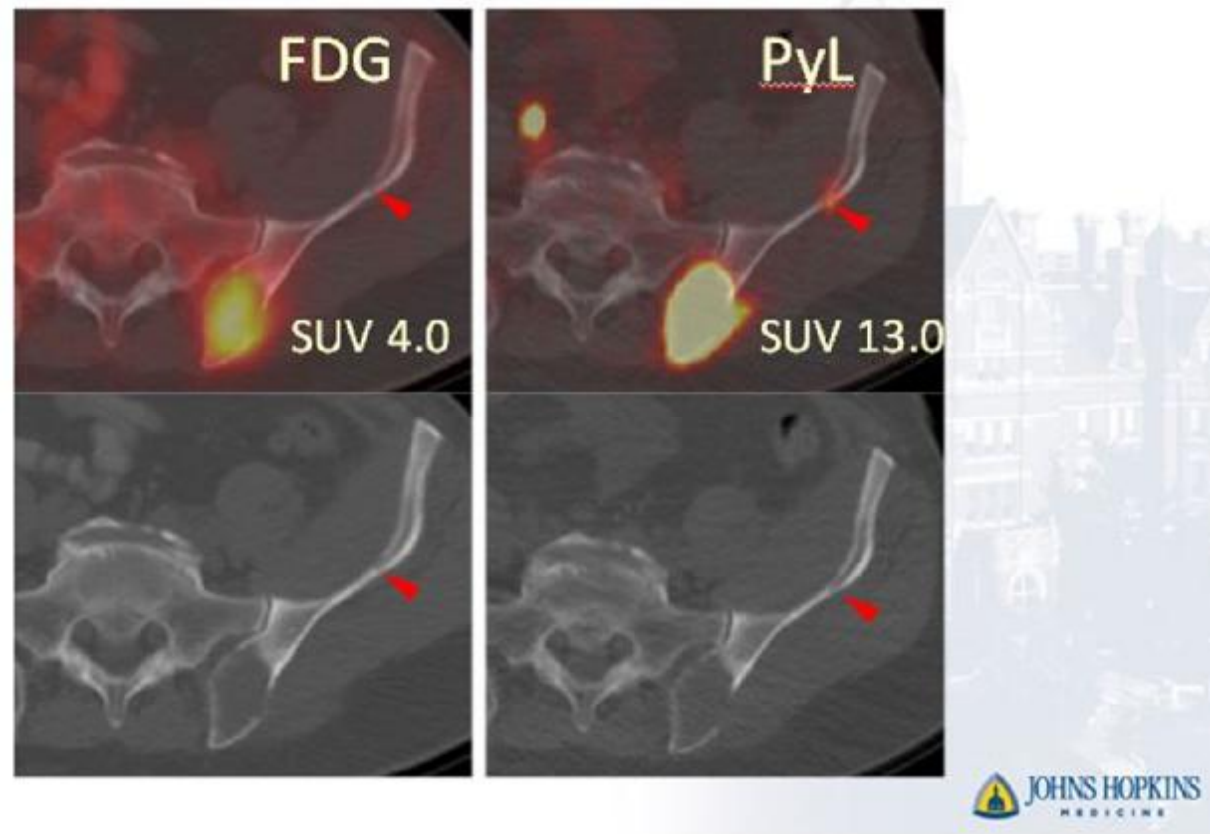


PSA = 0.1

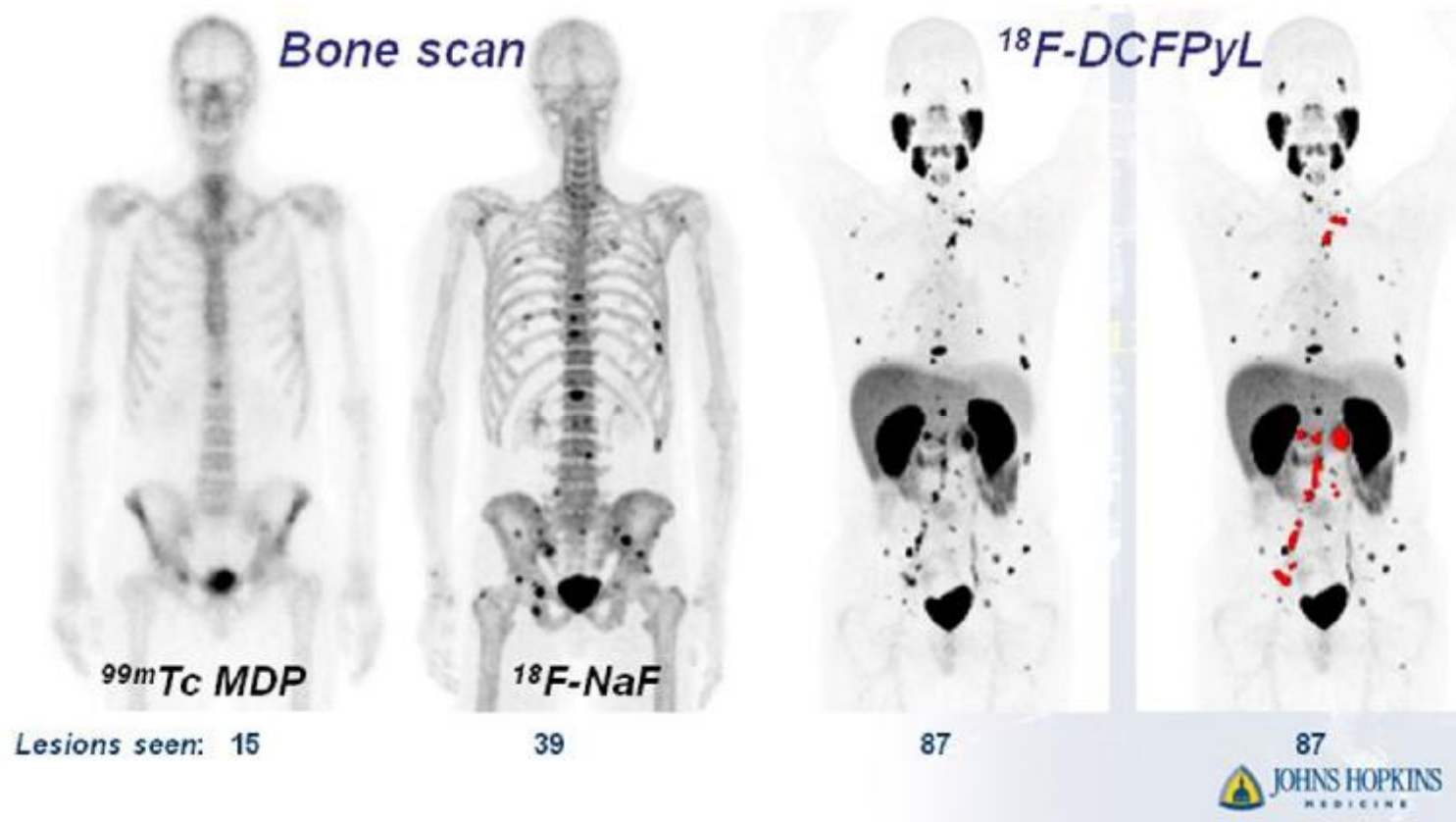
^{18}F -DCFPyL compares favorably to
 ^{68}Ga -PSMA
both images same patient



PSMA-targeting in ccRCC: Comparison to FDG



^{18}F -DCFPyL compares favorably to bone scan all images same patient



^{18}F -DCFPyL PET

Summary and conclusions

- Can be used for primary and metastatic prostate cancer in a wide variety of clinical scenarios.
- Can be used in other cancers in addition to prostate with trials in renal cell, breast and brain ongoing.
- Arguably the most sensitive method for detection of prostate cancer with imaging.

^{68}Ga -PSMA PET/CT positivity in Paget disease in patients with prostate cancer

Paget disease is a common disorder effecting up to 3% of elderly

Endothelial expression of PSMA in neovasculature known to occur in Paget disease

has been postulated as the mechanism causing the ^{68}Ga -PSMA PET/CT positivity of this condition

Paget disease should be taken into consideration when ^{68}Ga -PSMA PET/CT is used during workup of patients with prostate cancer so that this pitfall is avoided.

Prostatic tissue ectopia

World Journal of Surgical Oncology 2012;10:186 DOI: 10.1186/1477-7819-10-186. Tan et al.

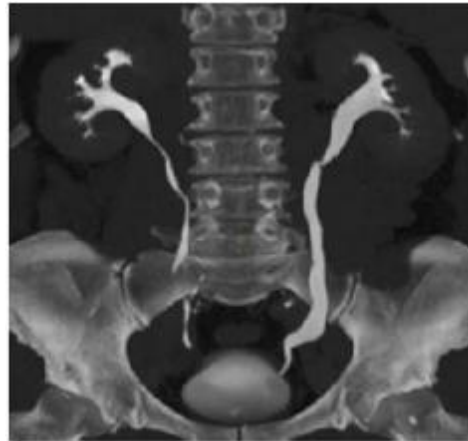
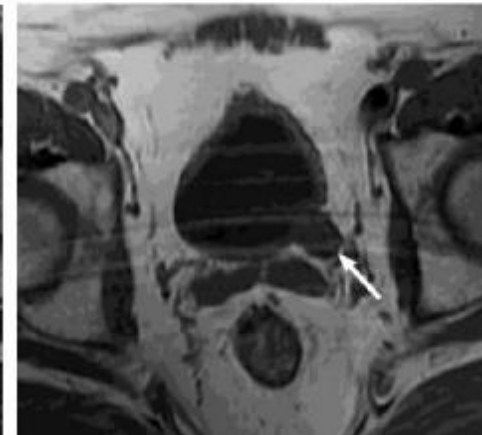
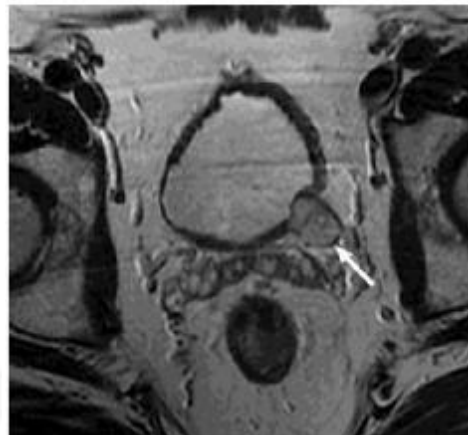


Fig. 1A



Fig. 1B



Prostatic tissue ectopia

Ectopic prostatic tissue is an unusual but not uncommon finding in the genitourinary tract.

Aberrant prostatic tissue occurs most commonly in the urethra (20%) and urinary bladder (80%), but has also been observed in the testis, epididymis, penis, cervix, and

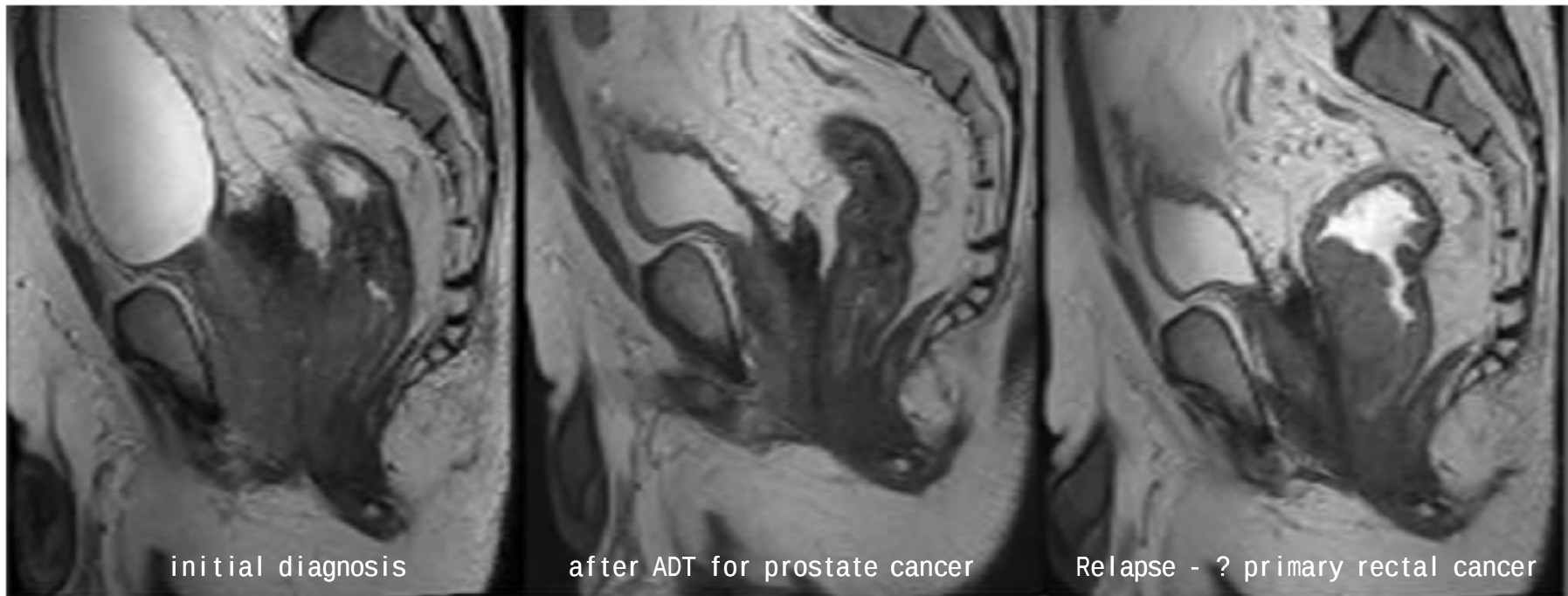
Vagina (McCluggageWG, et al.; Ectopic prostatic tissue in the uterine cervix and vagina: report of a series with a detailed immunohistochemical analysis. (2006) Am J Surg Pathol 30:209 – 215).

Ectopic prostatic tissue in the lower female genital tract is almost certainly a benign condition, based on the morphology, including the presence of a double cell layer, although follow-up of larger numbers of cases is required. Possible theories of histogenesis include a developmental anomaly, metaplasia of preexisting endocervical glands, and derivation from mesonephric remnants.

American Journal of Surgical Pathology: February 2006 - Volume 30 - Issue 2 - pp 209-215.

World Journal of Surgical Oncology 2012;10:186 DOI: 10.1186/1477-7819-10-186. Tan et al.

metastatic 'poorly differentiated prostate cancer' with rectal invasion
Androgen-deprivation therapy (ADT)



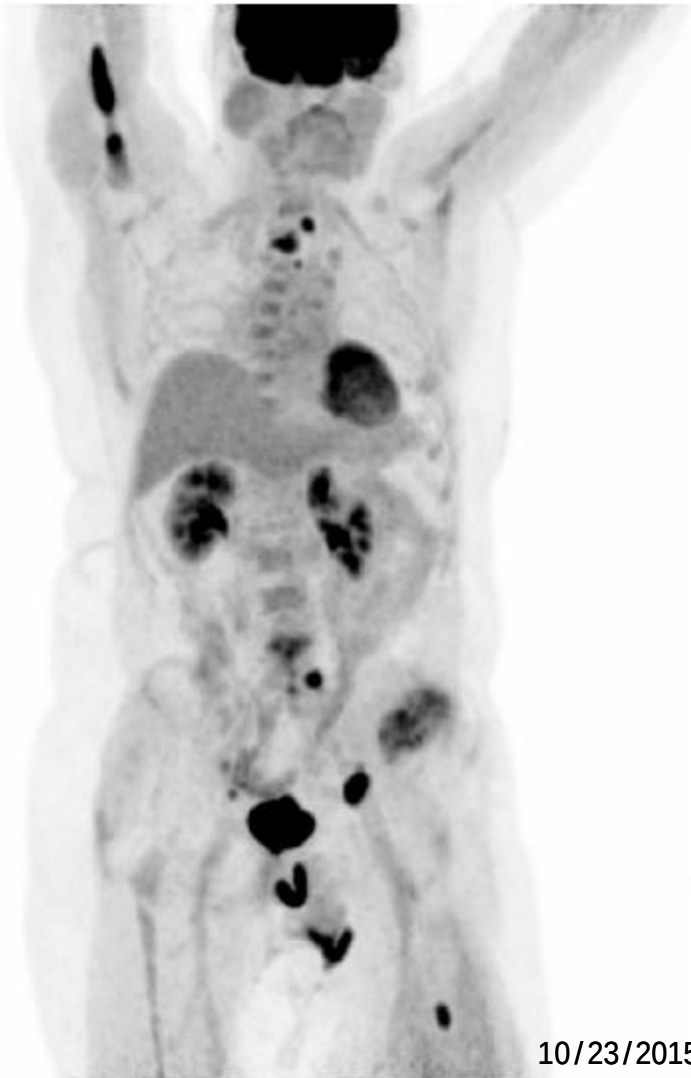
Poorly differentiated prostate cancer shows the highest incidence of rectal invasion, possibly due to tumor dedifferentiation or gene aberration. Diagn Pathol 2014; 9: 35

Increased AR expression and signaling despite AR blockade are most frequently associated with subsequent castration resistant growth of prostate cancer. Nat Med 2004; 10: 33-39.

Similarly, a metastatic poorly differentiated prostate cancer may mimic a primary anal cancer at the perianal skin after ADT.

(AR): Androgen Receptor

metastatic castration-resistant prostate cancer (mCRPC)



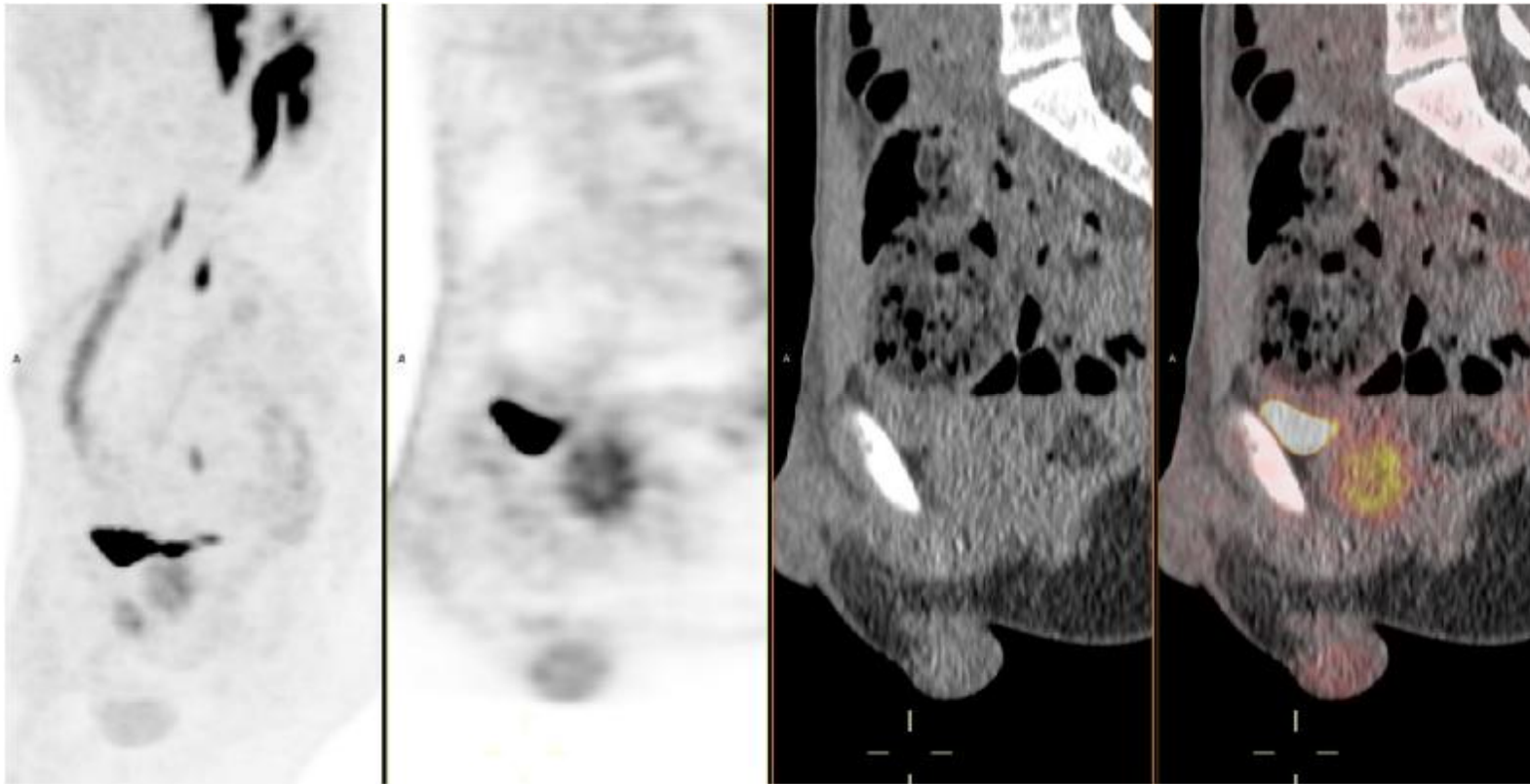
67-year-old gentleman with mCRPC s/p multiple courses of RT, most recently CK SBRT to T2 (3000cGy/5Fx, 5/2014) and palliative RT to the left femur (800cGy/1Fx, 12/2014).

Restaging MRI of T/L spine demonstrated progressive disease within the T11 vertebral body, for which he was treated T10-T12 to 2000 cGy in 5 fractions completed 2/25/15.

PET INDICATION: Subsequent anti-tumor treatment strategy.

1. FDG focus in surgical bed in region of seminal vesicles - local recurrence.
2. FDG activity of chest, abdomen, and pelvic Lymph node metastasis.
3. FDG avid osseous lesions - distant skeletal metastasis.

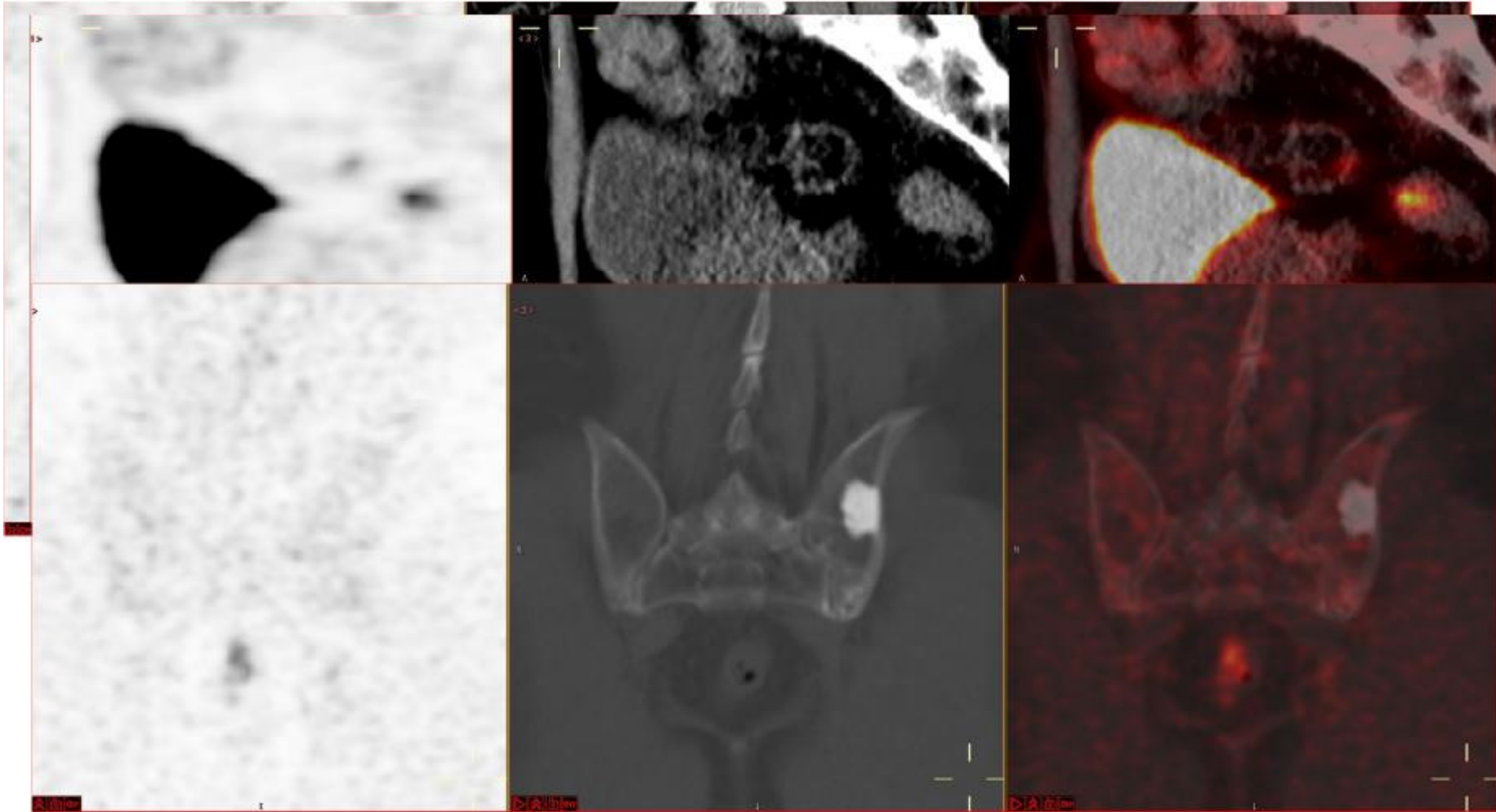
Metastatic Prostate Cancer



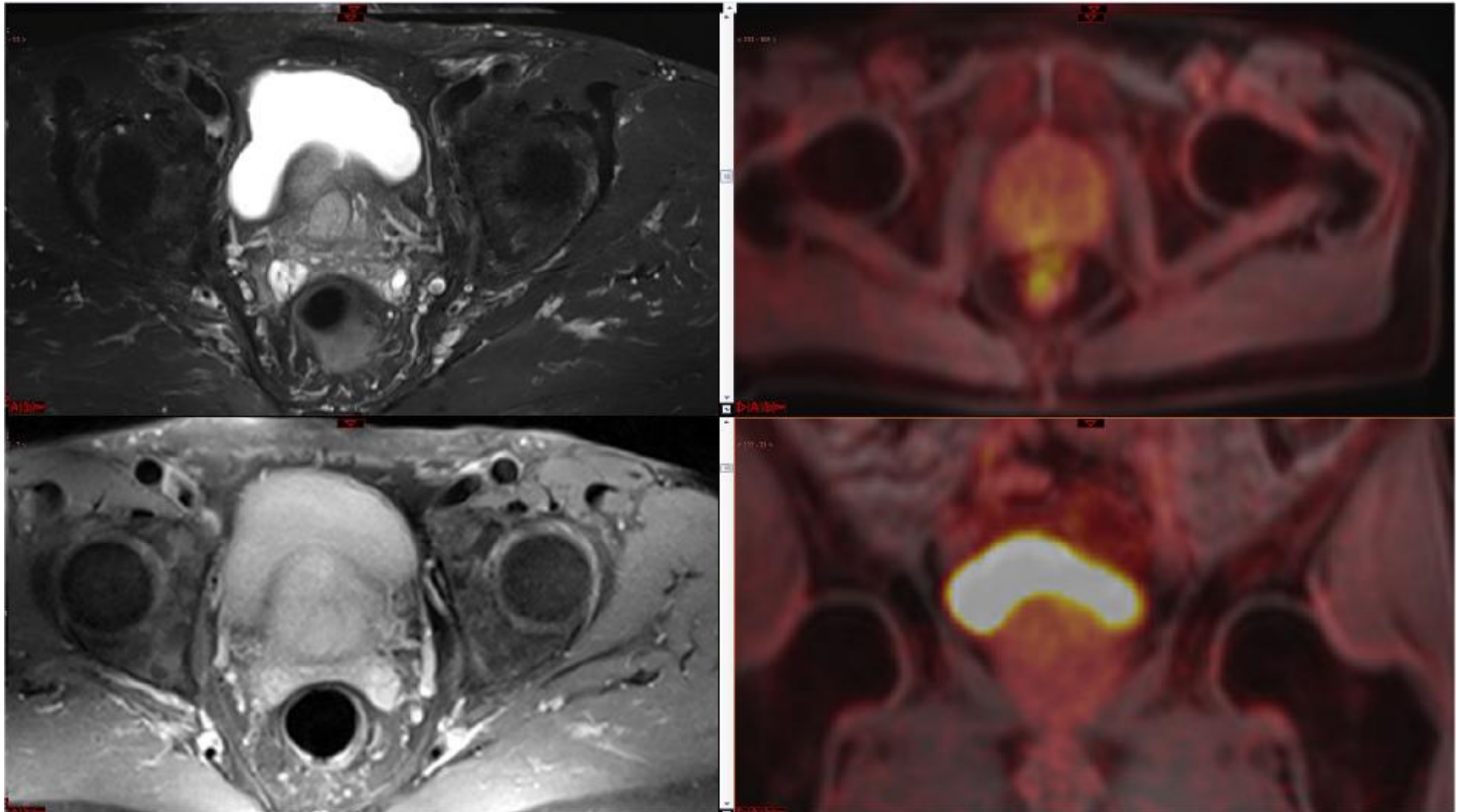
17 y.o male with medullary thyroid carcinoma and MEN type 2B. He is status-post a complete thyroidectomy and lymph node dissection; has hx of metastatic intracranial lesion of the left parietal lobe and received 20 G of stereotactic gamma knife therapy on April 23, 2008.

CT 1.16.2014: Enlarging hyper enhancing 4.0 x 2.5 cm metastatic mass on the left side prostate.
Biopsy 2.6. 2015: Skin, left lateral chest; prostate: Metastatic medullary carcinoma of the thyroid.

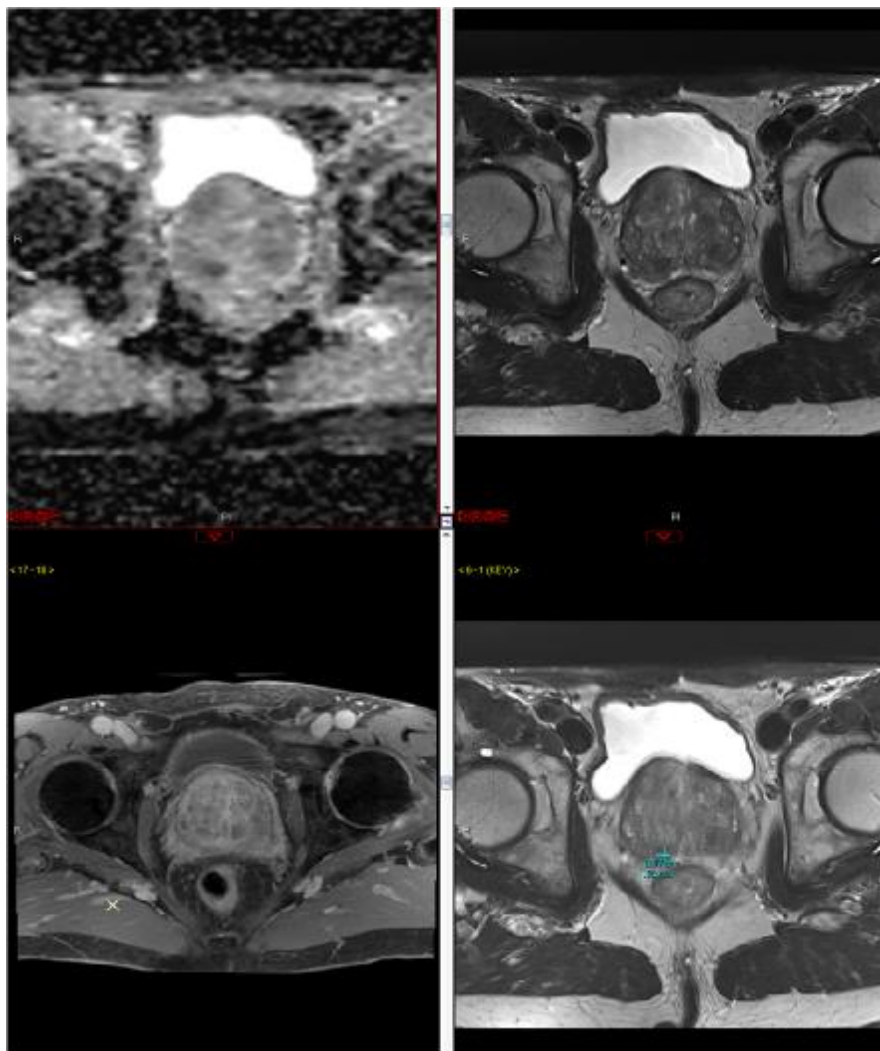
^{18}F FDG PET-CT Prostate Cancer



^{18}F FDG PET-MRI Prostate Cancer



^{18}F FDG PET-MRI Prostate Cancer



Diagnostic MRI when his
Biopsy was performed at
JHH

PET Radiotracers in Urological oncology

Prostate cancer	Biological analog	Function	Measured effect	Indication
^{18}F -FDG	Glucose	Glycolysis	Aerobic and anaerobic glycolysis, glucose consumption	Advanced prostate
^{11}C and ^{18}F -choline	Choline	Choline kinase	Cell membrane metabolism, tumor Proliferation	Staging, re-staging, response to therapy
^{11}C -acetate	Acetate	Fatty acid synthase	Lipid synthesis	Staging, re-staging, response to therapy
^{11}C -methionine	Methionine	A-A transport	Protein synthesis	Staging, re-staging, response to therapy
^{18}F -FDHT	Testosterone	Androgen receptor	Measures androgen receptor	Metastatic prostate cancer, hormone refractory
anti- ^{18}F -FACBC		A-A transport		Metastatic prostate cancer
^{18}F -DCFPyL ^{68}Ga -PSMA		PSMA		*Staging, re-staging, response to therapy
^{18}F -NaF	Fluoride	Bone mineralization	Measures bone status	Metastatic PC, evaluation of bone disease

The uptake of the thymidine analogue 30-deoxy-30-[^{18}F] fluorothymidine (^{18}F -FLT) correlates very well with malignant cell proliferation.

Future Perspectives

- Defined PET-MRI protocols need to be developed and validated which go beyond adding two imaging modalities. If the question is lesion characterization and either PET or MRI has already sufficiently answered the question, the full range of MRI sequences applied to dedicated organ protocols might not be necessary.
- Further improvements in the MRAC are essential to provide accurate quantification of regional PET tracer uptake, which is important for treatment monitoring, specifically for early prediction of treatment response.
- An important potential future of PET-MRI might be in the use of non-FDG tracers, which might allow monitoring of individualized treatment decisions.
- A major task will be to explore and determine the value of combined functional, quantitative(?), and morphologic imaging in MRI with simultaneous molecular and metabolic information from PET.

Conclusions

PET with its inherent high sensitivity

- Utilizing various radiotracer agents pointing to multiple different tumor targets such as glycolysis; Hypoxia; Amino Acids, Malignant cell proliferation and AA transport; Ab-Ag; and receptors and
- Utilizing hybrid imaging technologies as in PET-CT,
 - PET-MRI technology is capable ofmore successfully imaging urologic malignancies and prostate cancer, which results in better patient care and outcome.



Relative Sensitivity of Imaging Technologies

Molecular Oncology 2 (2008) 115-152

Thank You



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Abstinence before prostate MRI offers benefits in over 60s 3/3

	Abstinence less than 3 days (g1 = 42)	Abstinence 3 days or more (g2 = 42)
SV vol	6 mL	8.8 mL
Mean interpretability	2.0	2.5
Nondiagnostic (N/d) scores	10-13 (23.8% to 31%)	2-5 (4.7% to 11.9%)
N/d for men over 60*	9-11 of 25 (36% to 44%)	2-5 of 26 (7.6% to 19.2%)
N/d for men 60 & under	1-2 of 17 (5.8% to 11.7%)	0 of 16 (0%)