Imaging mCRPC

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ESMO Asia Singapore 2015

Disclosures: active 2015

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Employee	None
Consultant	None
Major Stockholder	None
Speakers Bureau	Siemens Healthcare, Janssen
Honoraria	Siemens Healthcare, Janssen
Scientific Advisory Board	Siemens Healthcare

Presentation includes discussion of the off-label use of drugs and equipment

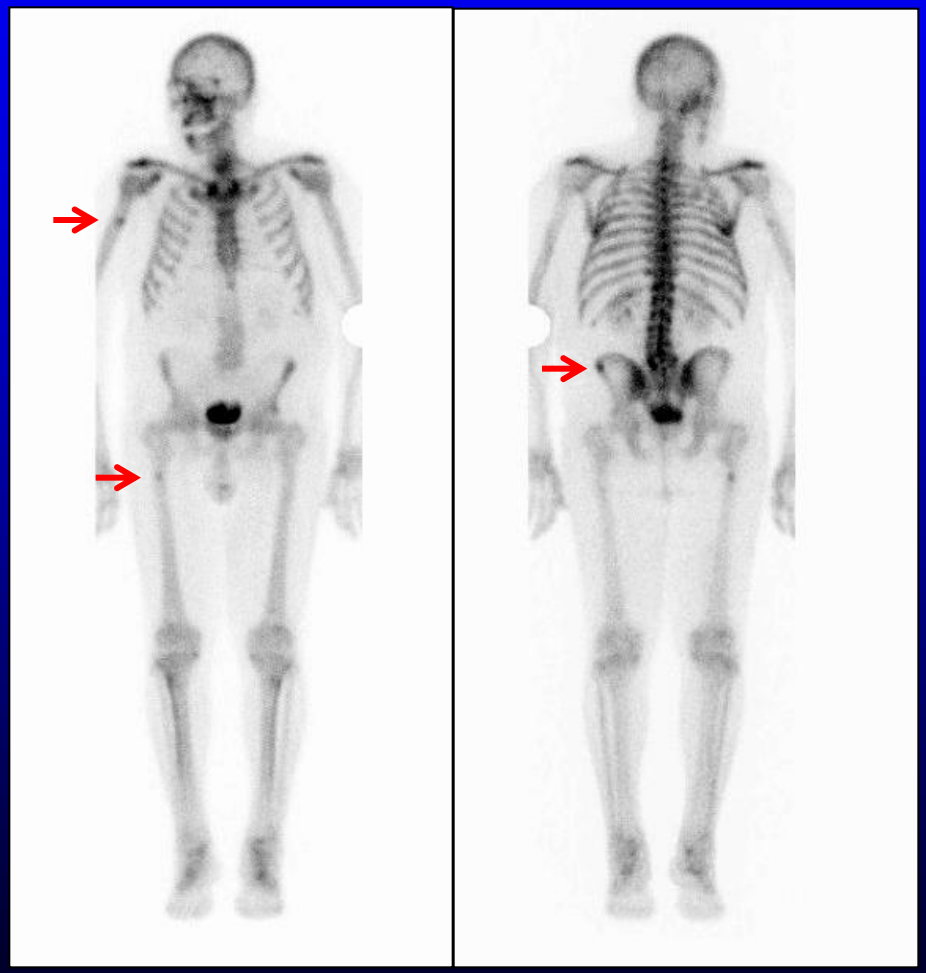
Current imaging methods leads to poor confidence for assigning clinical states & therapy benefits

- Limited imaging tools
  - Unable to accurately predict which patient has metastatic disease
  - Predict who will / will not benefit from targeted treatments
  - Identify who is not benefiting early after starting treatment
- Limited targeted therapies effectiveness
  - Late detection of metastatic disease (M0 →M+ →M++)
  - Volume & heterogeneity of response are not considered in Rx prescriptions
  - Failure to rapidly progress patients through standard therapies so they become eligible for clinical trials

74 mCRPC on Enzalutamide. PSA 0.4 ng/ml.

How many BS lesions consistent with metastases?

Is this patient suitable for ablative therapy for early M+?



04Oct13

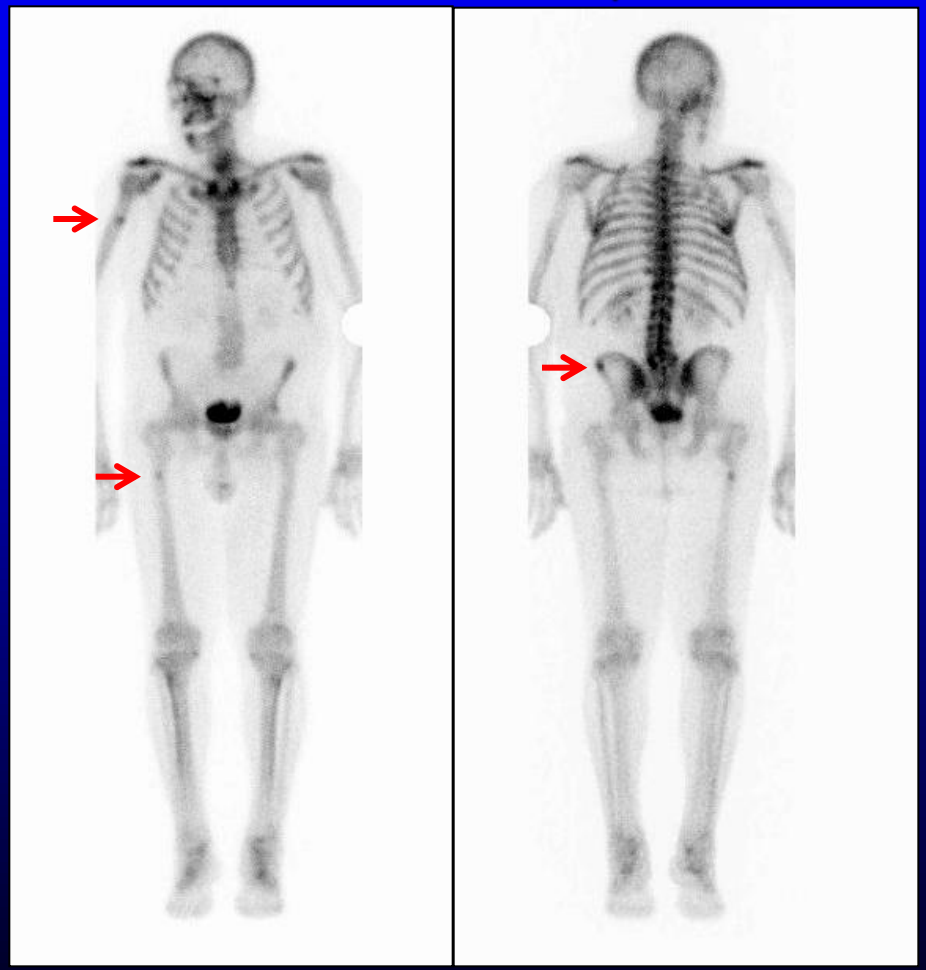
Is the BS good enough to assign this state as oligometastatic (≤3-4 lesions)?

01Oct13

WB-MRI detects more malignant lesions/ patient than bone scans

74 mCRPC on Enzalutamide. PSA 0.4 ng/ml

3 lesions on planar bone scan; 6 lesions on WB-MRI



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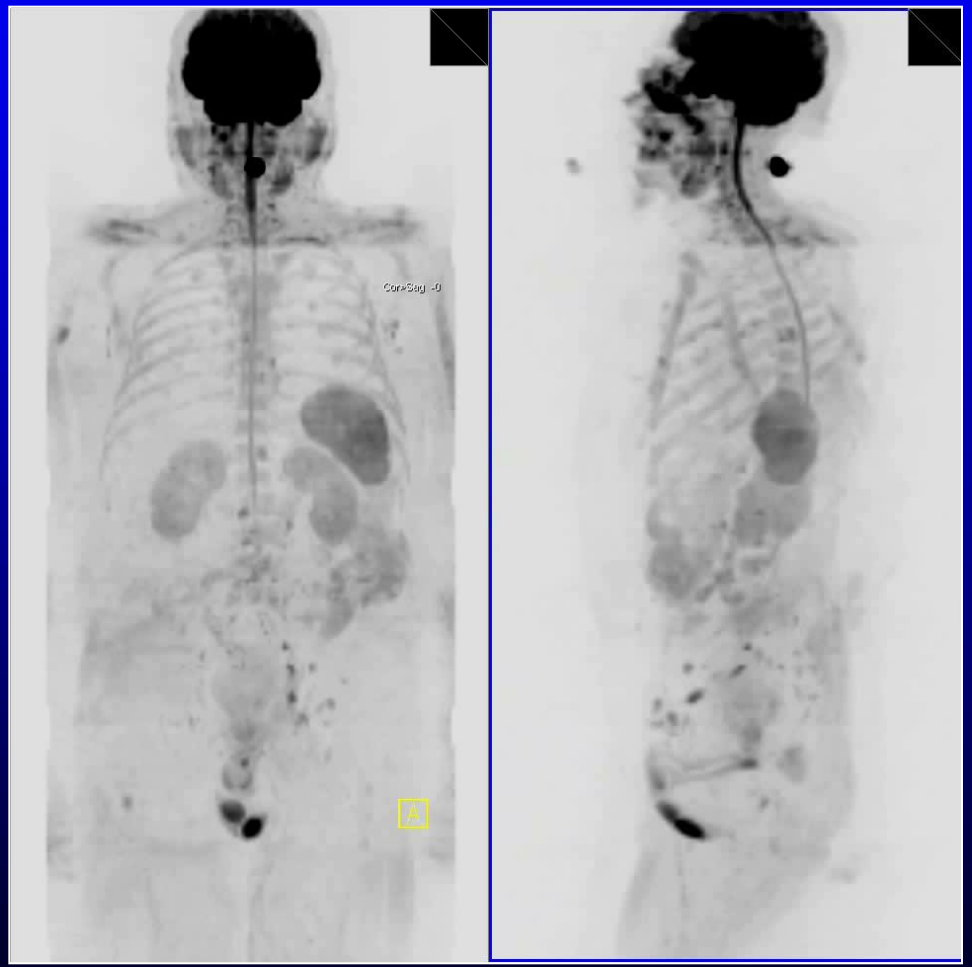

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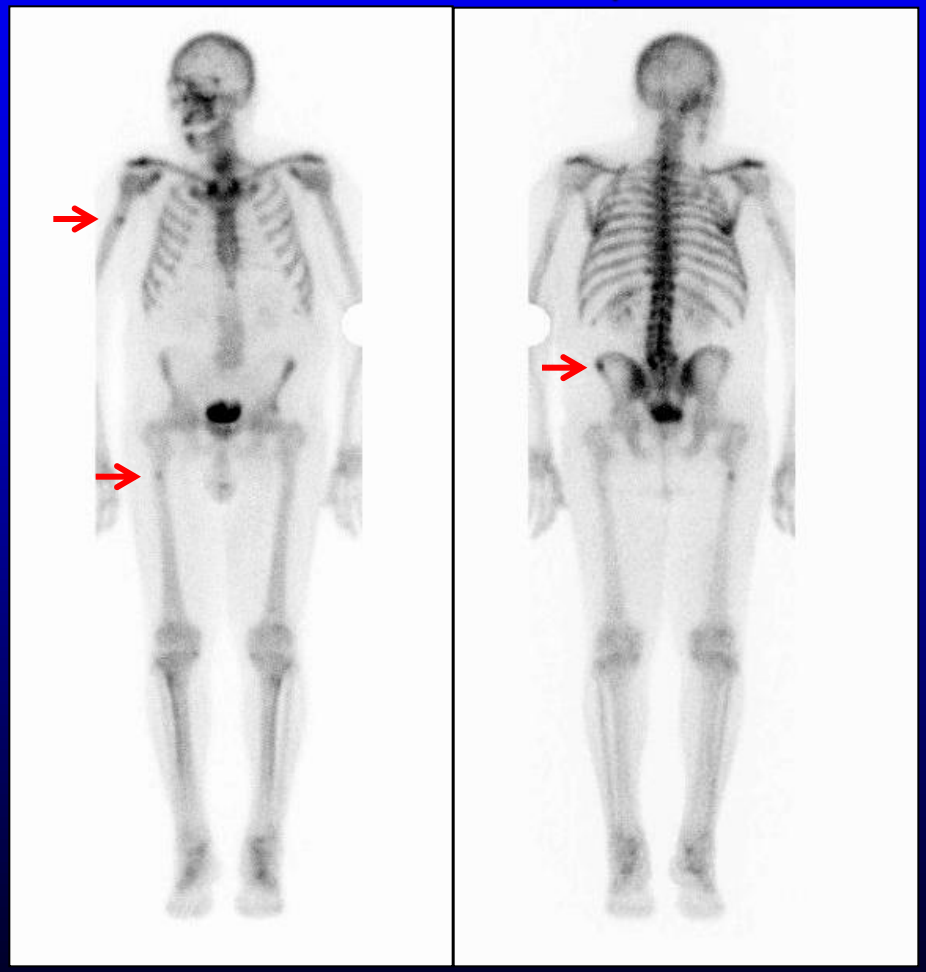

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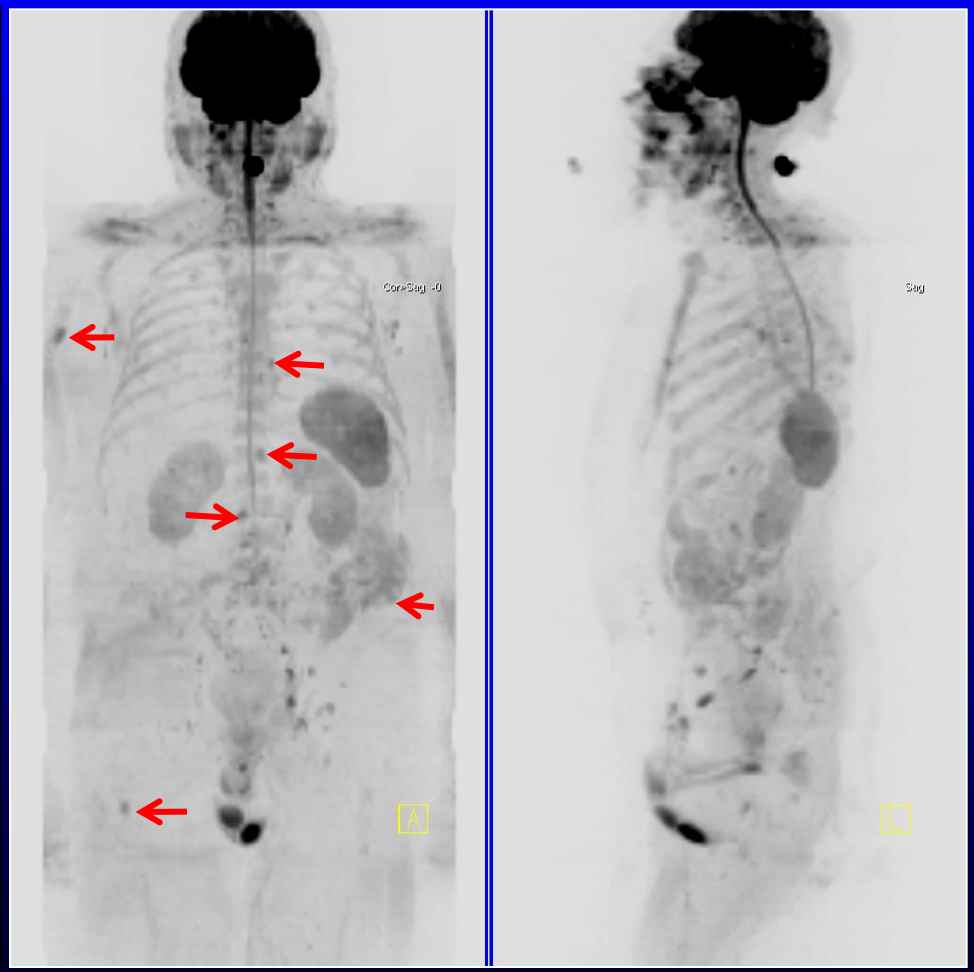


01Oct13

WB-MRI outperforms bone scans in detecting bone metastases & is as good as CT for lymph node evaluations

- 1
- 5
- M
- M

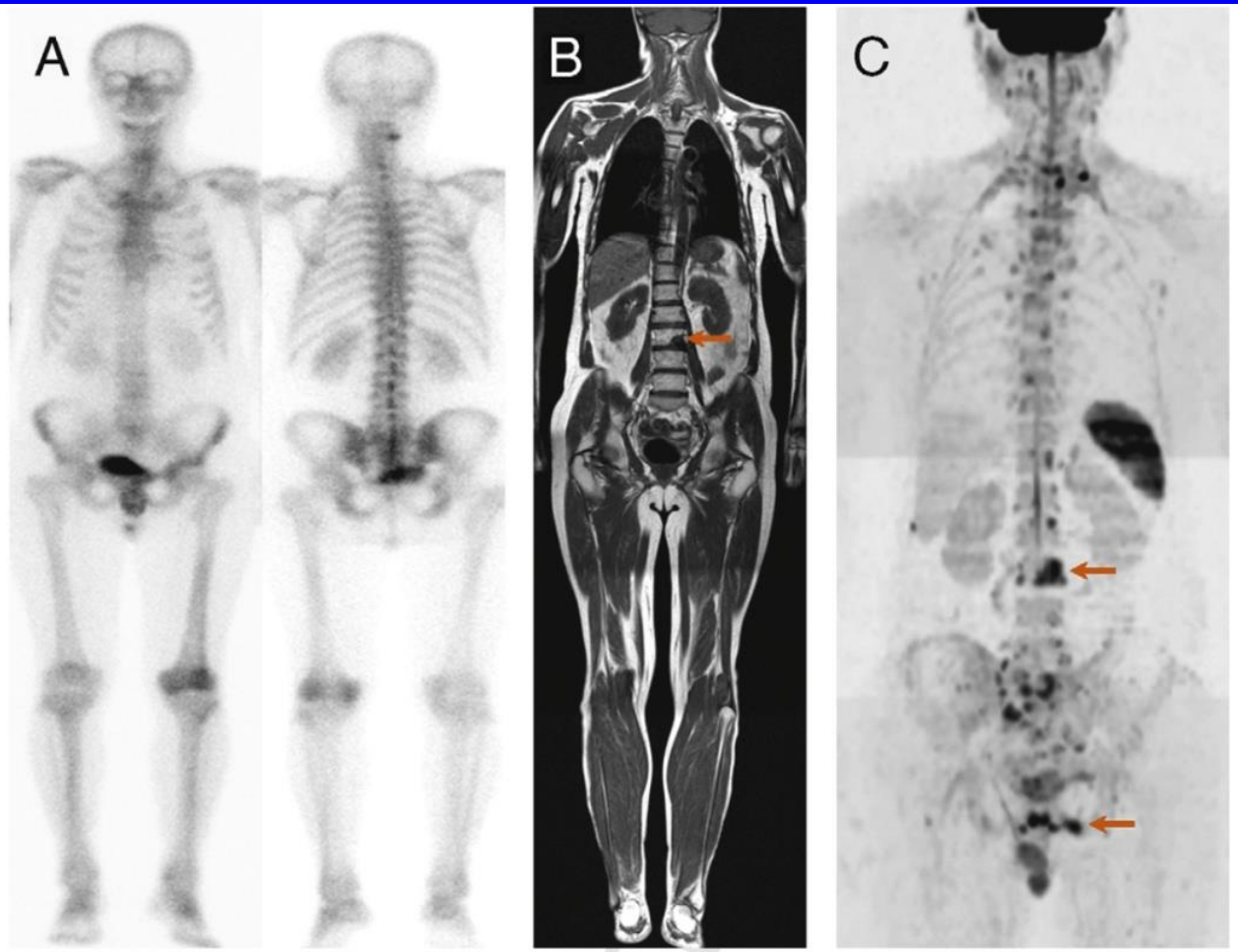


Fig. 2 – Whole-body magnetic resonance imaging (MRI) versus false-negative bone scintigraphy (BS) for bone metastasis detection in a 65-yr-old patient with newly diagnosed prostate cancer (prostate-specific antigen 18 ng/ml; Gleason score 7 [4 + 3]). (A) BS (anterior-posterior and posterior-anterior views) shows no significant lesion. (B) Coronal T1 and (C) diffusion-weighted MRI images of the whole body confirm bone metastases within L3 and the left iliac bone (arrows).

ents

Lymph	
CT	7
WB-M	7
Bone	
BS + x	
WB-M	00

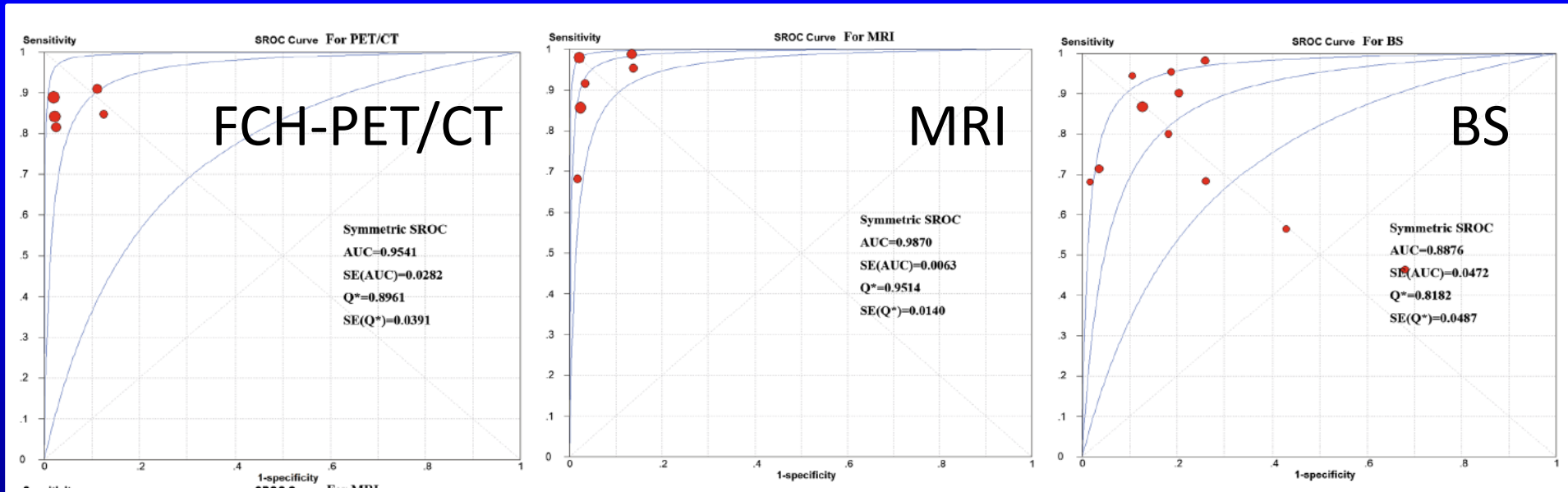
Lecouve raphy for

Choline-PET/CT, MRI, and planar bone scan for bone metastasis detection in prostate cancer

	Studies	Sensitivity % (95% CI)	Specificity % (95% CI)	DOR	AUC
Per patient analysis					
FCH-PET/CT	5	87 (87-93)	97 (93-99)	150.7	0.95
MRI	6	95 (90-98)	96 (92-98)	343.2	0.98
Bone scan - planar	11	79 (73-93)	82 (78-85)	20.3	0.89
Bone scan (prospective)	*6*	*76 (69-82)*	*80 (74-84)*	*12.7*	*0.85*
Bone scan (retrospective)	*5*	*86 (76-92)*	*84 (79-89)*	*35.3*	*0.92*

Shen G, Deng H, Hu S, Jia Z. Comparison of choline-PET/CT, MRI, SPECT, and bone scintigraphy in the diagnosis of bone metastases in patients with prostate cancer: a meta-analysis. Skeletal Radiol. 2014 Nov;43(11):1503-13.

Choline-PET/CT, MRI, and planar bone scan for bone metastasis detection in prostate cancer



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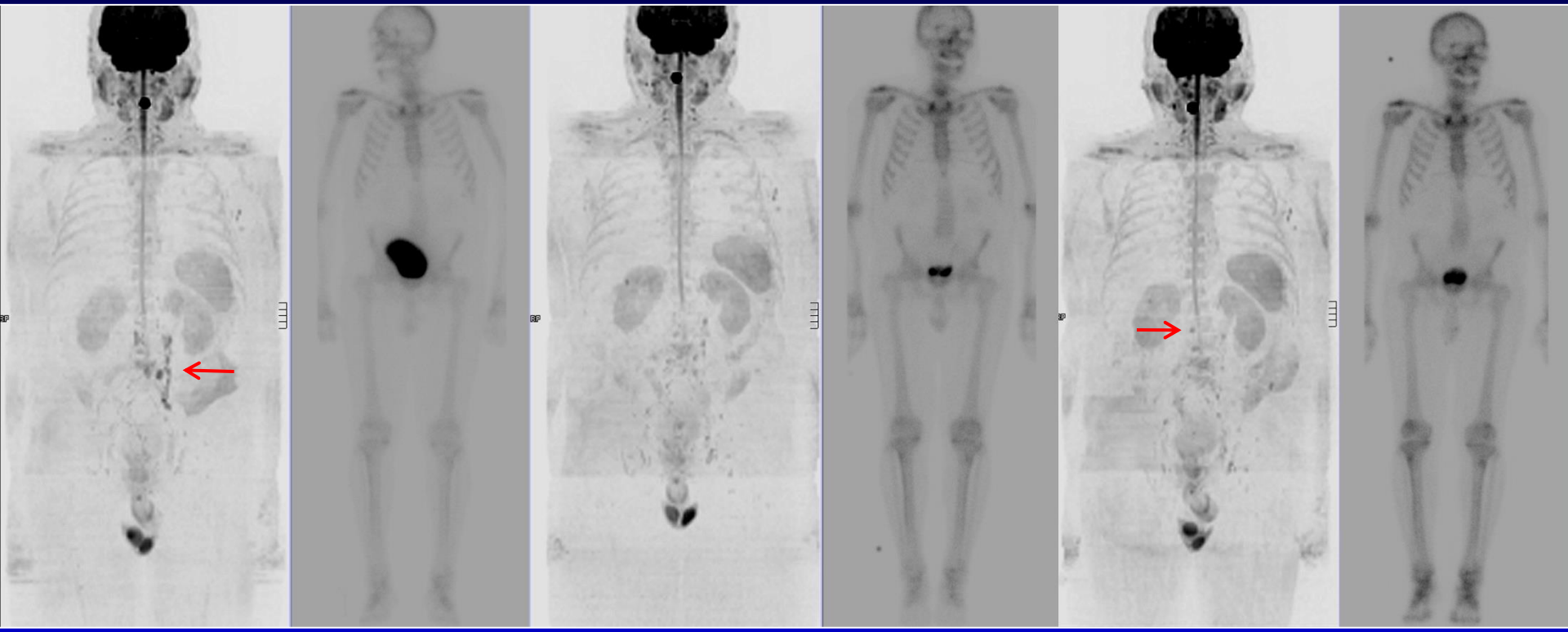
Metastatic CRPC. Rx Enzalutamide

Screening PSA 45.5	Week 13 PSA 0.6	Week 25 PSA 0.3



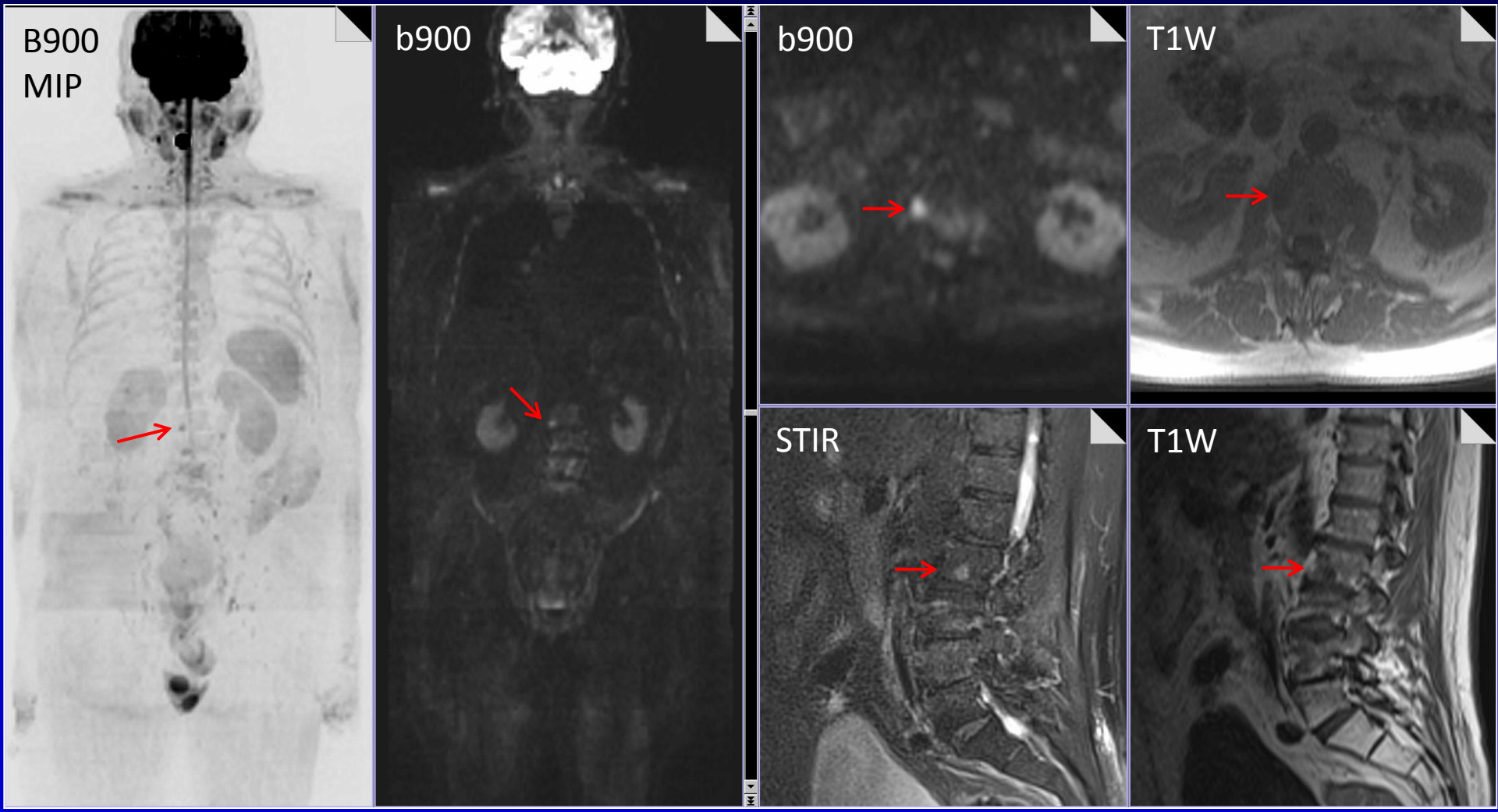
Retroperitoneal nodes.
WB-MRI - no bone metastases
BS = no lesions

Retroperitoneal nodes improved.
WB-MRI = no lesions
BS = no lesions

Retroperitoneal nodes improved.
WB-MRI = 1 new bone metastasis
BS = no lesions

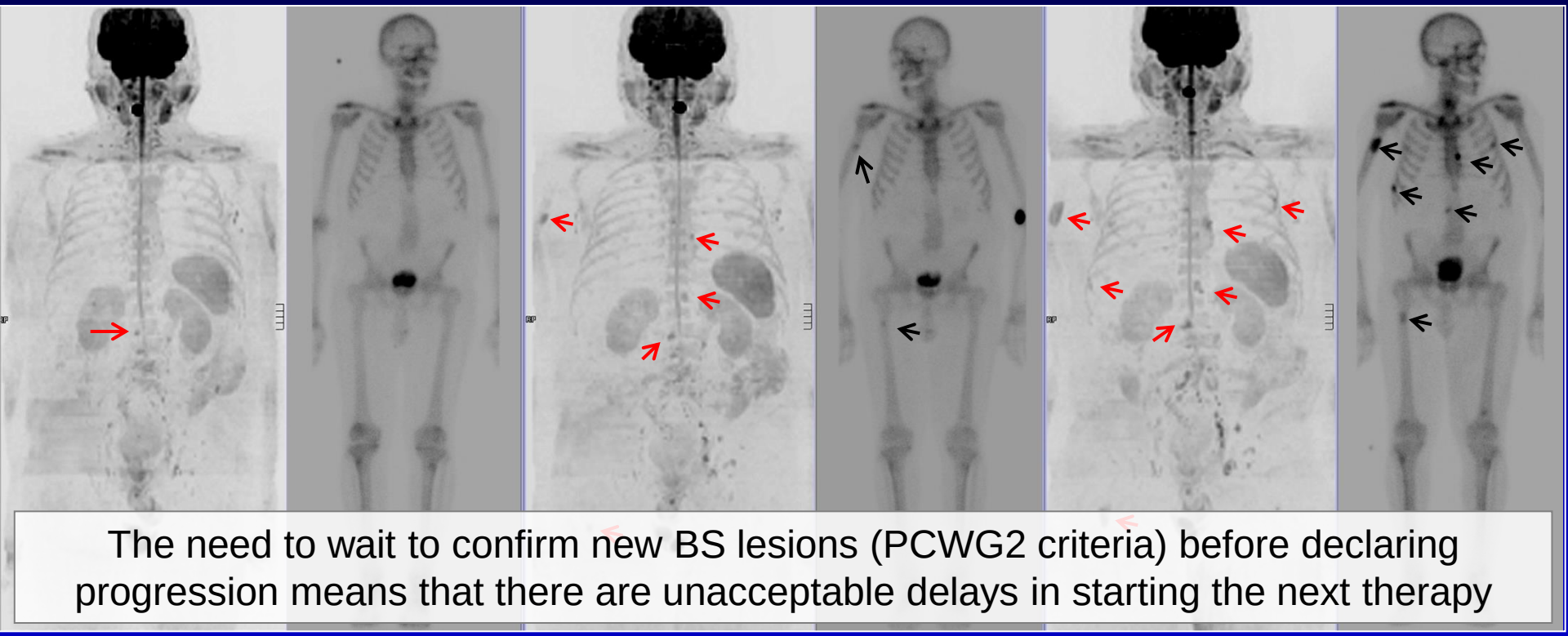
Metastatic CRPC. Rx Enzalutamide

Week 25; PSA 0.3 ng/ml



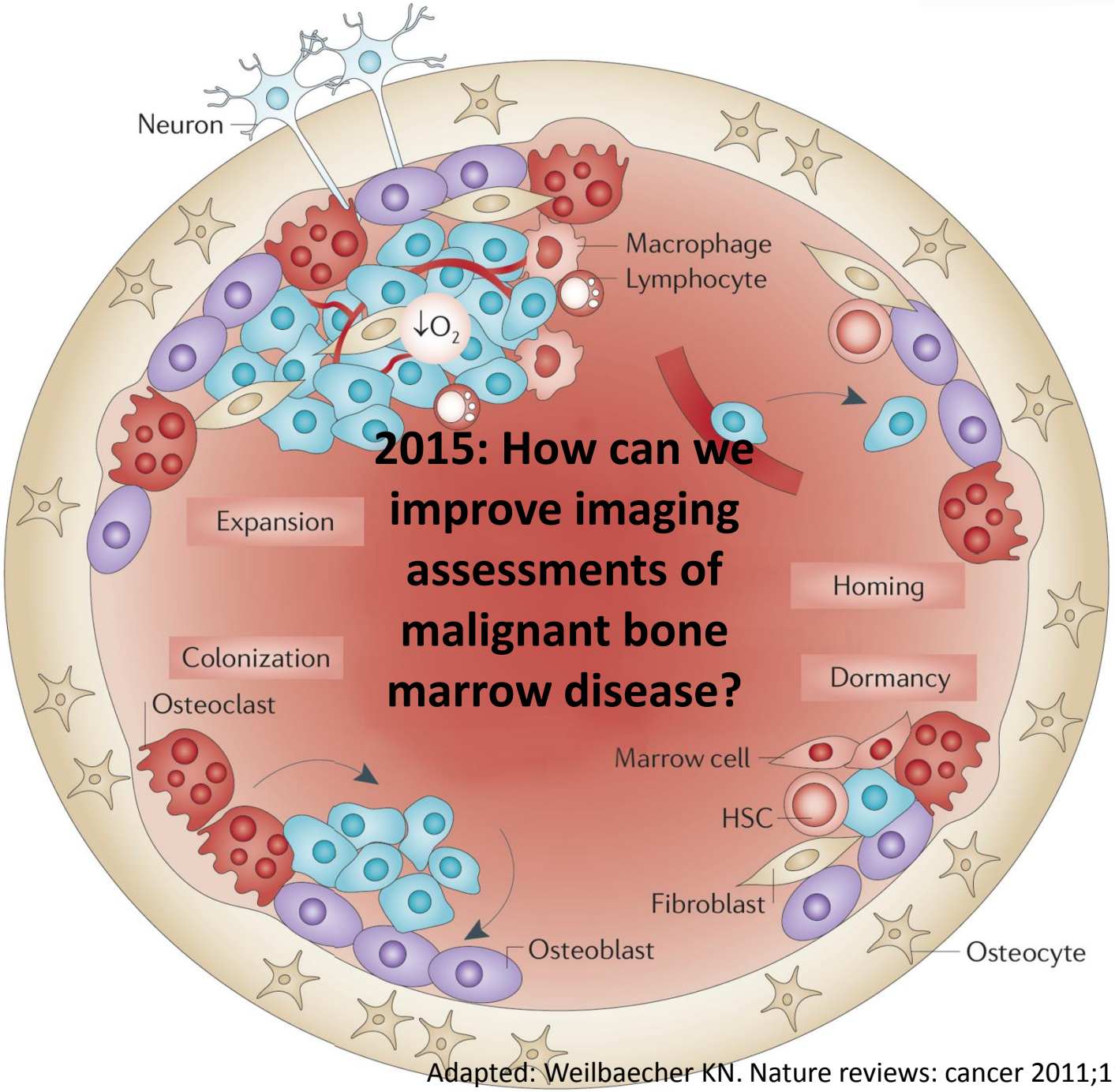
Rx Enzalutamide

Actual date of progression	Recorded date of progression	Progression confirmed date
Week 25 PSA 0.3	Week 37 PSA 0.4	Week 49 PSA 1.5



The need to wait to confirm new BS lesions (PCWG2 criteria) before declaring progression means that there are unacceptable delays in starting the next therapy

Retroperitoneal nodes improved. WB-MRI = 1 new bone metastasis BS = no lesions	Retroperitoneal nodes worse. WB-MRI = 5 bone lesions BS = 2 lesions (outside flare period; needs confirmation)	Retroperitoneal nodes progressing. New lymphoedema. WB-MRI = 7 bone lesions BS = 7 lesions (1 on posterior projection)



2015: How can we improve imaging assessments of malignant bone marrow disease?

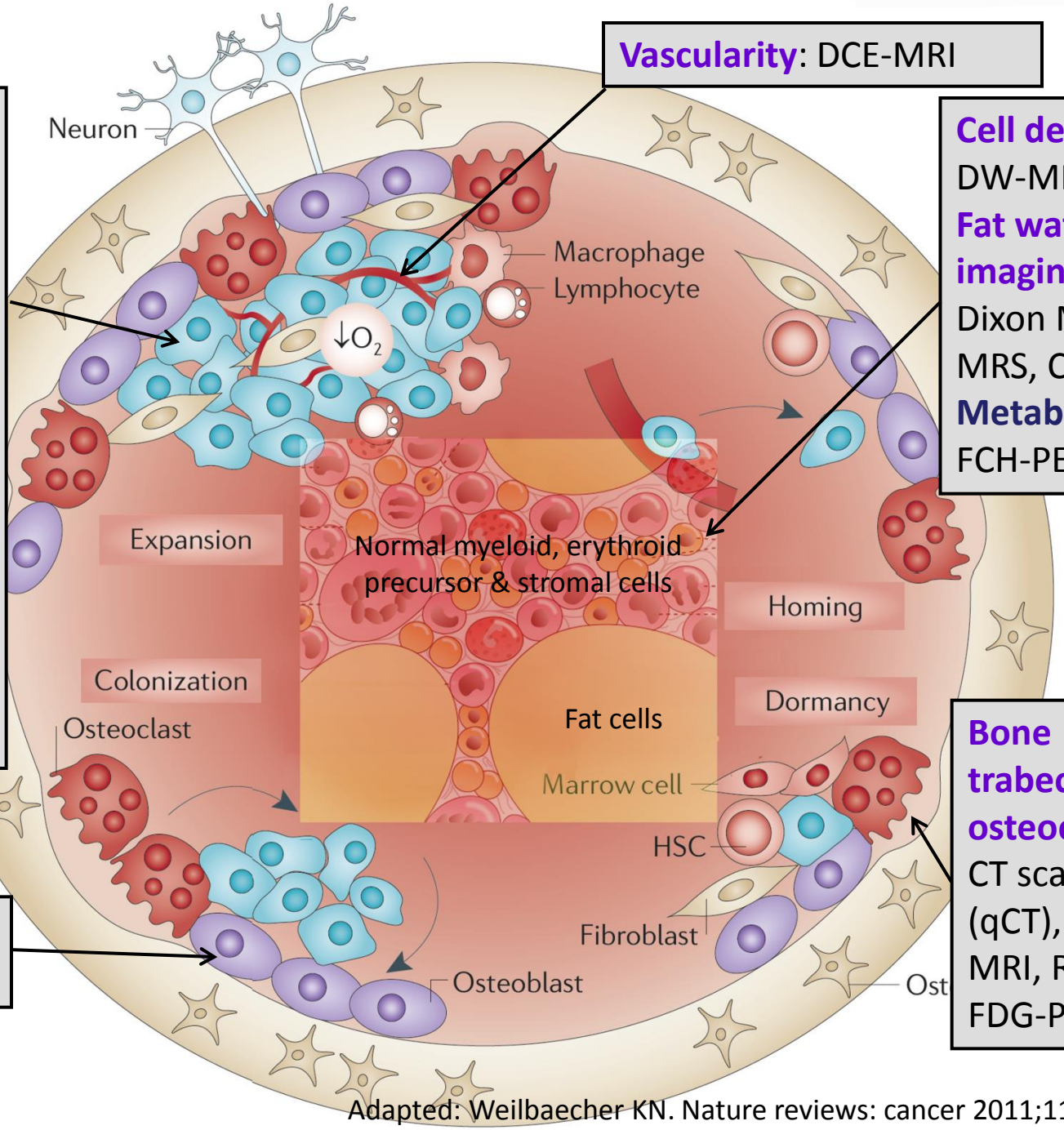
Adapted: Weilbaecher KN. Nature reviews: cancer 2011;11:411-25

Vascularity: DCE-MRI

Tumor cell surface & cytoplasmic receptors (specific): F-DHT, labelled antibodies/ pharmacophores to PSA, Ga-PSMA

Tumor metabolism (non-specific): FDG, choline, acetate & methionine-PET

Cell density: DW-MRI
Fat water imaging: Dixon MRI, MRS, CT
Metabolism: FCH-PET



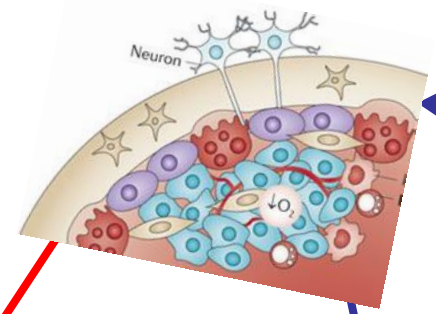
Osteoblasts: Bone scans, NaF-PET

Bone trabeculae & osteoclasts: CT scans (qCT), UTE-MRI, R2*, FDG-PET

Adapted: Weilbaecher KN. Nature reviews: cancer 2011;11:411-25

PCa - prostate; BrCa - breast;
LCa - lung; MM - Myeloma
DKK1 - dickkopf-1

Cancer cells in bone marrow



"Osteomimicary" processes leading to fibroblast & osteoblast proliferation with collagen & osteoid deposition & Ca^{2+} (delamination of normal bone occurs by ↑OPG:RANKL ratio)

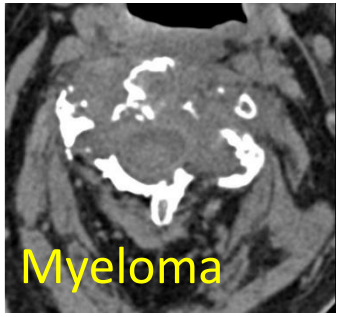
Growth factor(s)
Creates room for sclerotic lesions to grow (PCa, BCa)

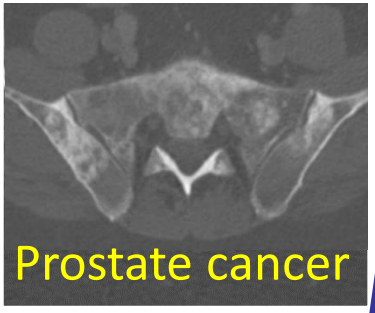
MM, LCa
[PCa, BrCa]

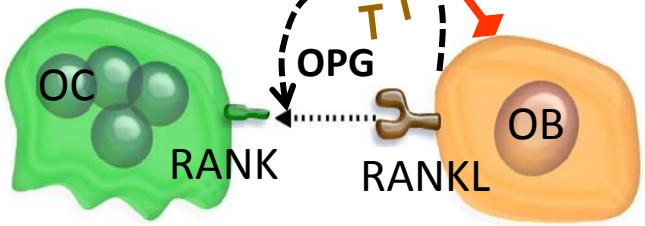
PCa, BrCa

Wnt pathway inhibitors, e.g., DKK1
(Multiple other osteolytic factors)

Upregulated Wnt pathways







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Osteolytic lesions.
Inhibition of bone formation & impair repair

Osteoblastic lesions.
Woven bone & osteosclerosis

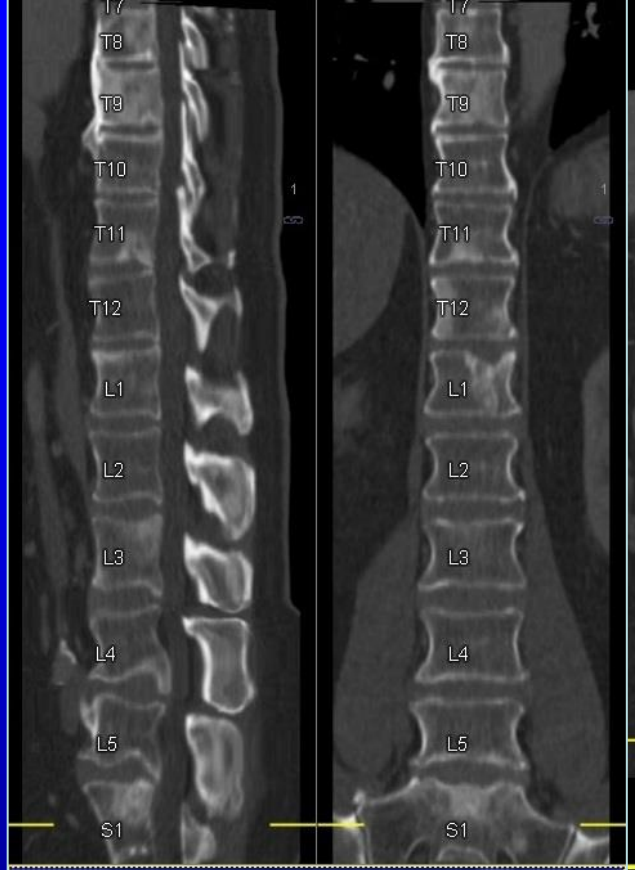
Major/edge osteoclast activation

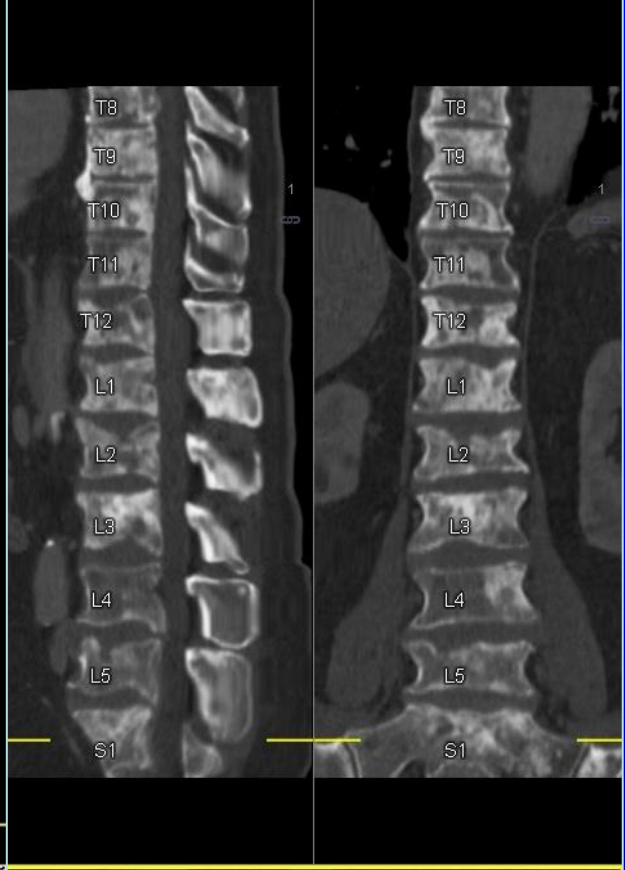
Altered OPG:RANKL ratio

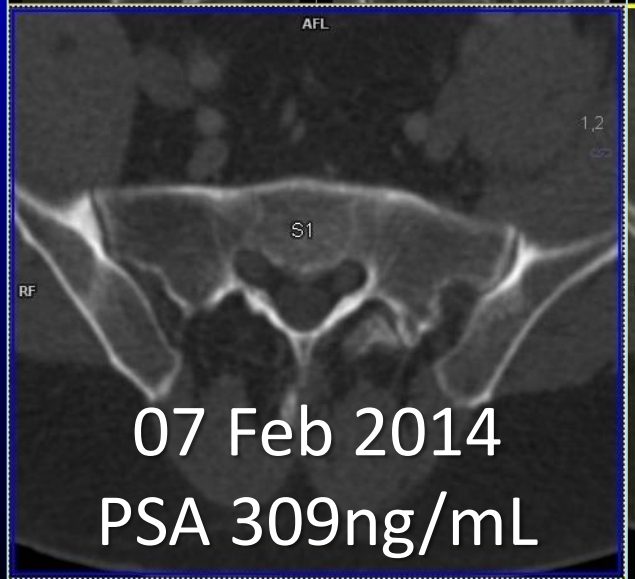
↑ osteoblast differentiation & function

Sclerotic progression of bone disease

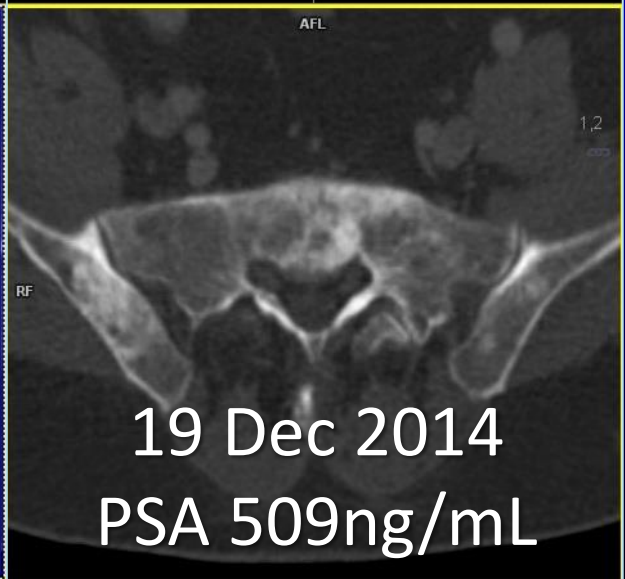
74 yo Rx Abiraterone
Increasing symptomatic with nausea and bone pain



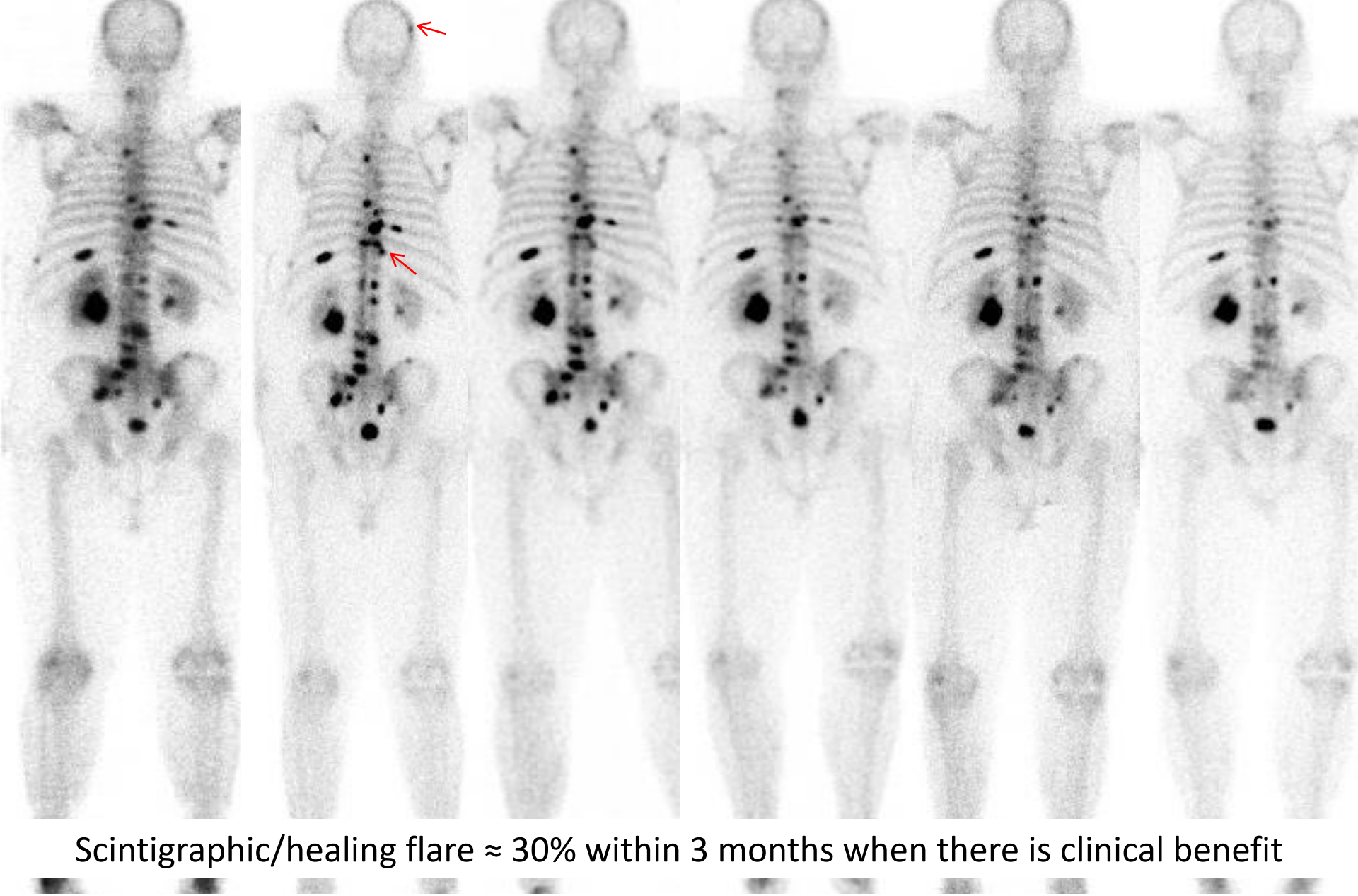




07 Feb 2014
PSA 309ng/mL



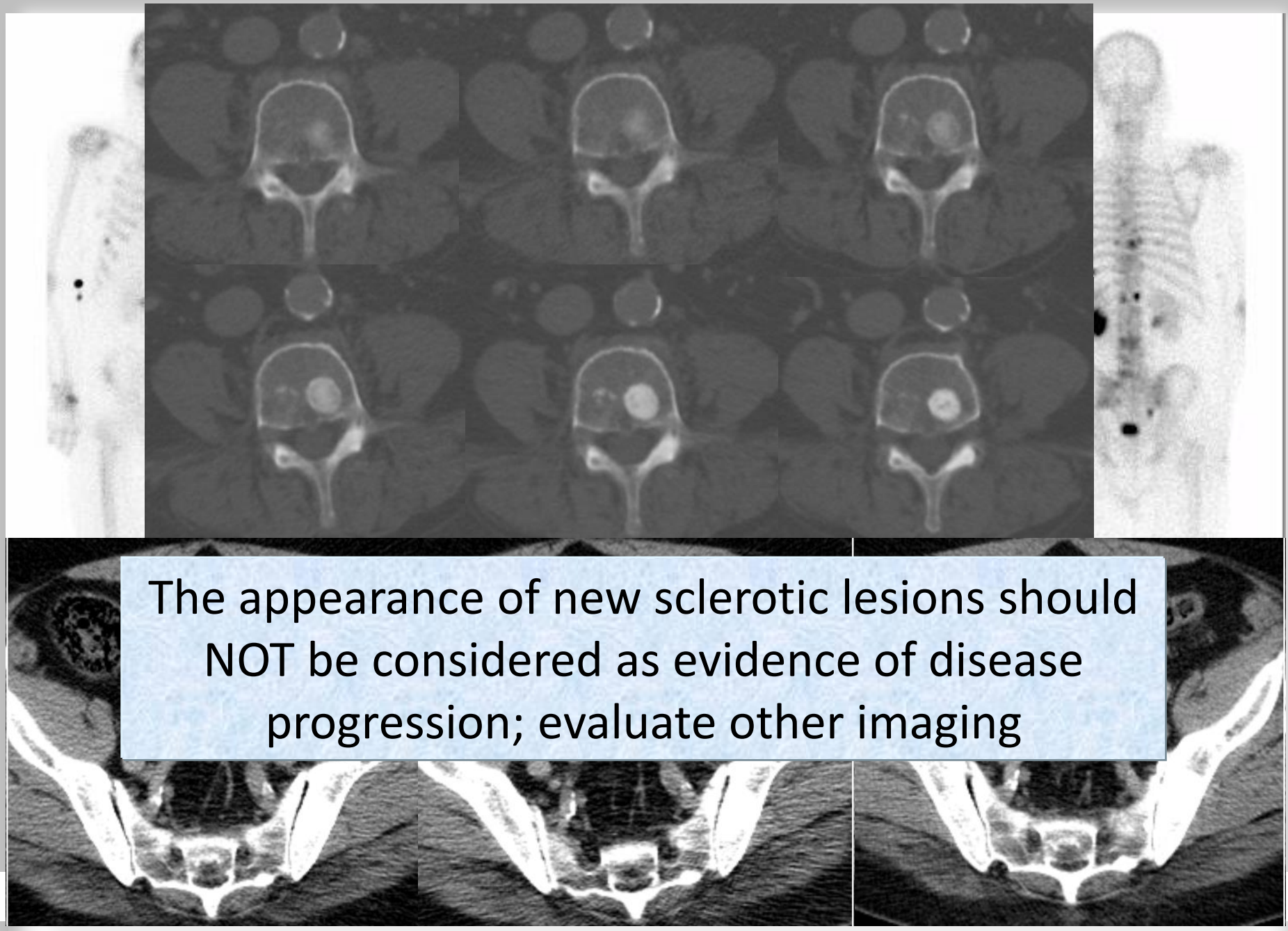
19 Dec 2014
PSA 509ng/mL



Scintigraphic/healing flare ≈ 30% within 3 months when there is clinical benefit

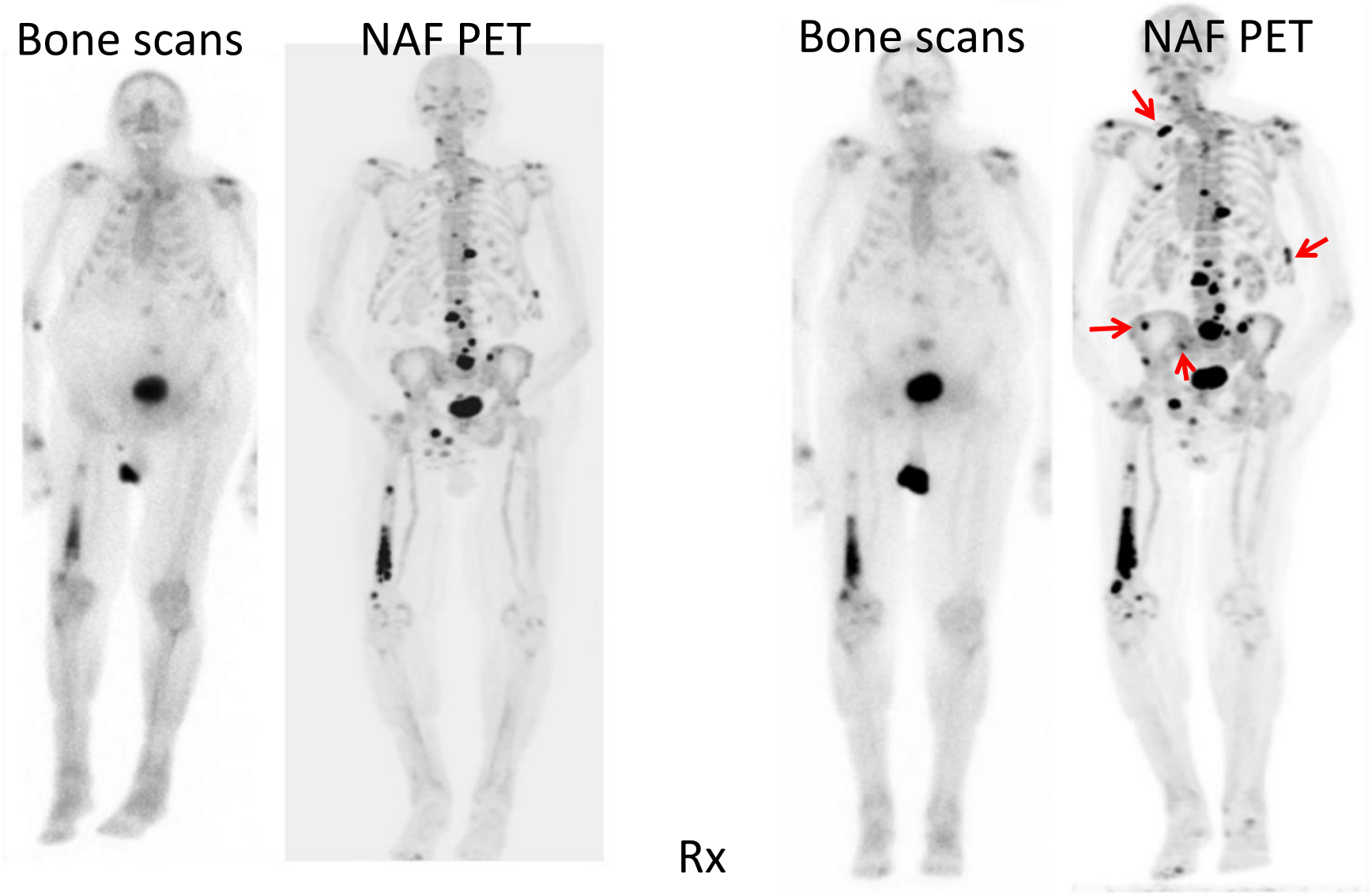
Images courtesy Courtesy Nina Tunariu & Johann de Bono: ICR, London

December 2011 February 2012 ….. Rx Enzalutamide continued → November 2012



The appearance of new sclerotic lesions should NOT be considered as evidence of disease progression; evaluate other imaging

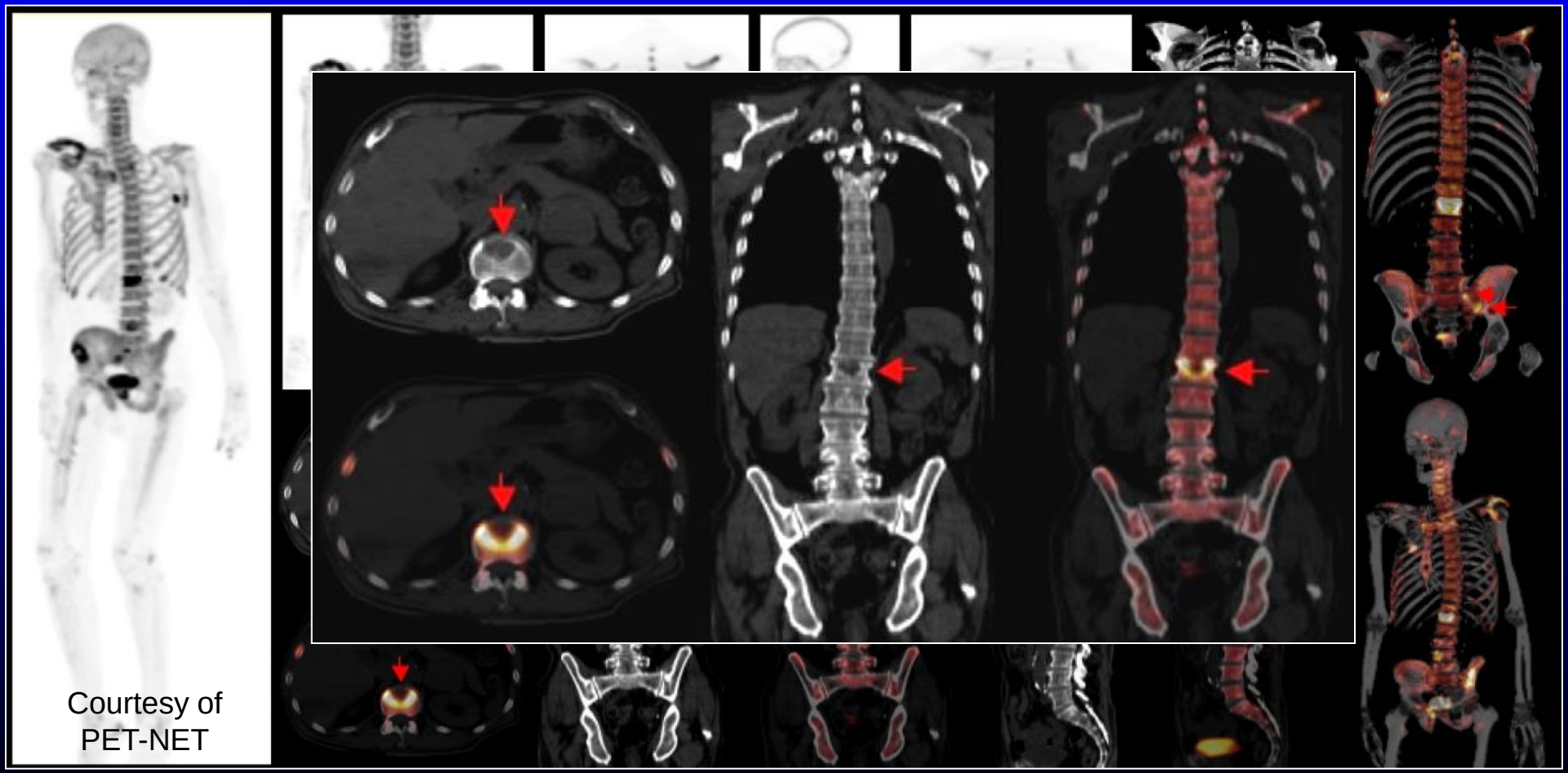
December 2011 53 years old male with mCRPC; Rx Enzalutamide November 2012



Morris MJ, et al. Seminars in Oncology 2013; 40:375-392

^{18}F-NaF PET-CT

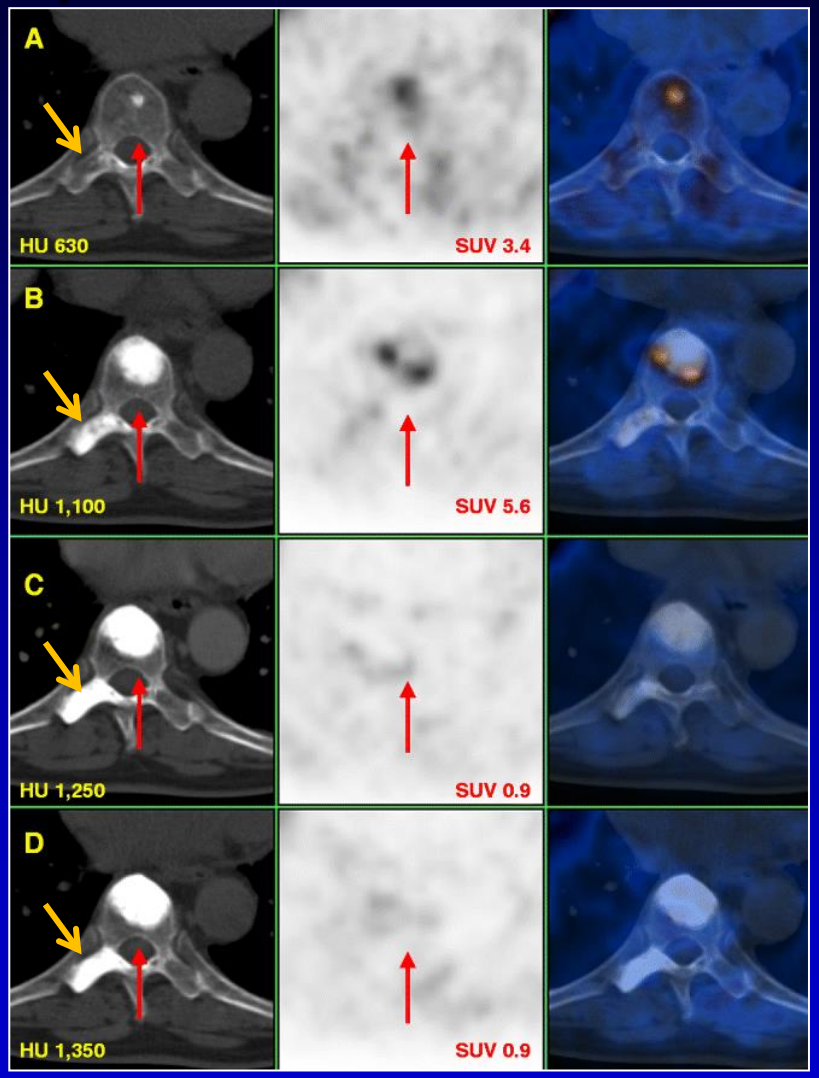
- CT component improves localisation & characterisation → reduces false positives
- No depiction soft tissue disease even if associated with bone metastases (↓)



Courtesy of PET-NET

Choline (CH) PET/CT for response assessments

- Evaluates cell membrane synthesis and degradation
- Higher uptake in lytic/ infiltrative than sclerotic disease. Densely sclerotic lesions (>825HU) are negative (?inactive)*
- 5 small studies suggests that FCH uptake decreases with successful therapy



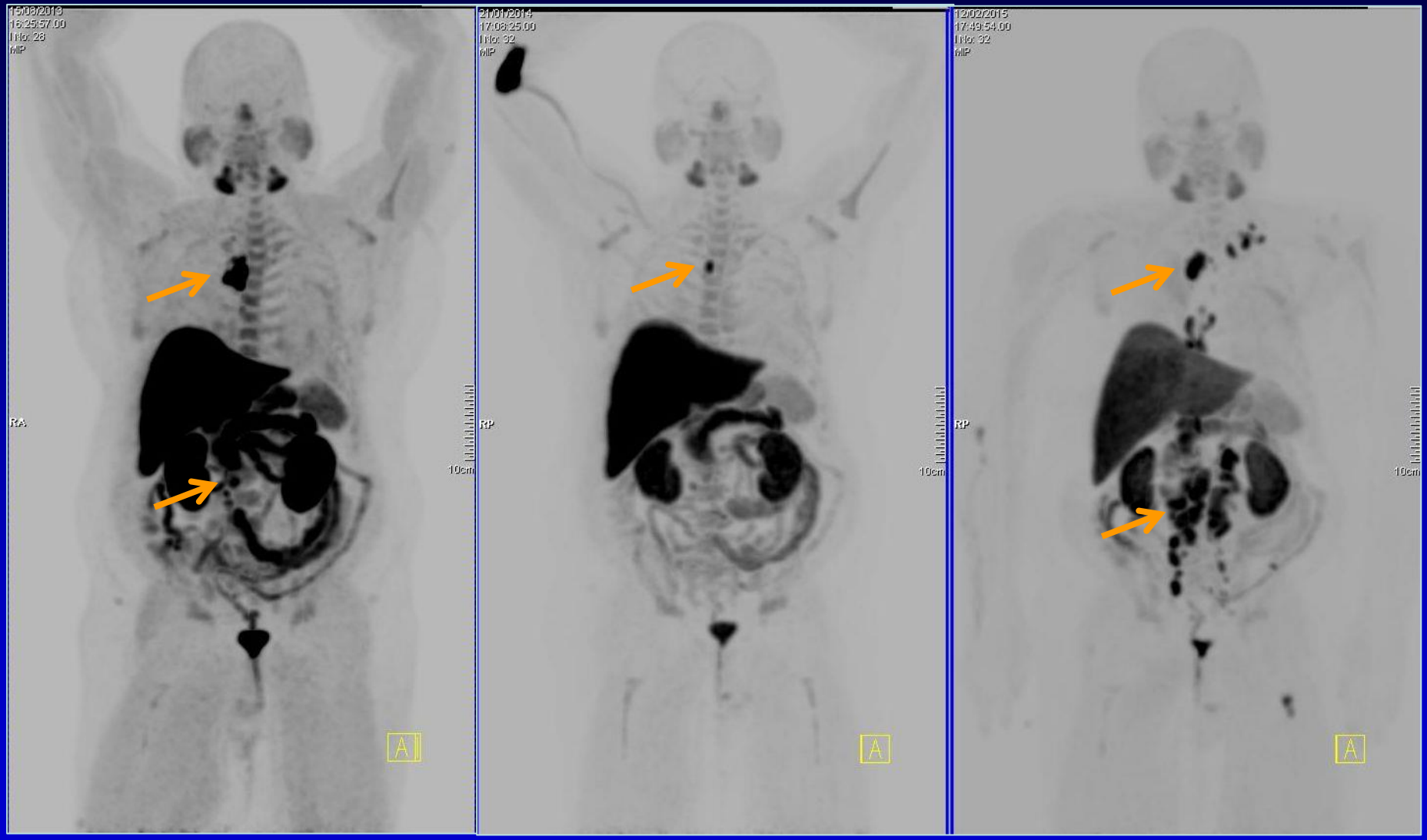
Bauman G, et al. (18)F-fluorocholine for prostate cancer imaging: a systematic review of the literature. Prostate cancer and prostatic diseases 2011; August: [Epub ahead of print]

*Beheshti M, et al. The Use of F-18 Choline PET in the Assessment of Bone Metastases in Prostate Cancer: Correlation with Morphological Changes on CT. Molecular Imaging and Biology. 2009; 11:446-454

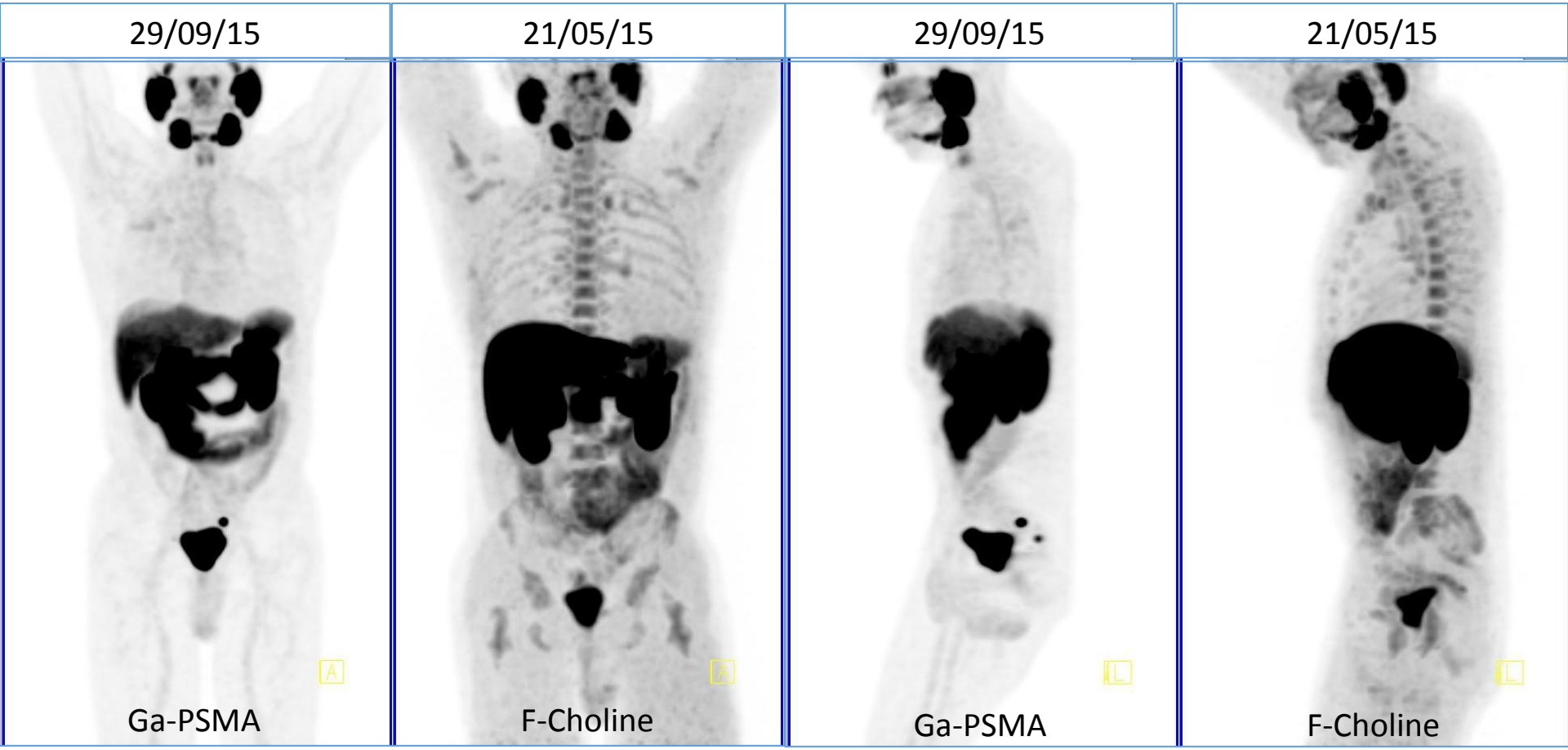
15Aug13
Post Docetaxel
PSA 5.2 ng/mL

21Jan14
x6 Carbizitaxel
PSA 3.2 ng/mL

12Feb15
Relapse
PSA 133 ng/mL



Ga-68 PSMA (specific) vs FCH (metabolic) biodistribution



Lower liver and bone marrow uptake

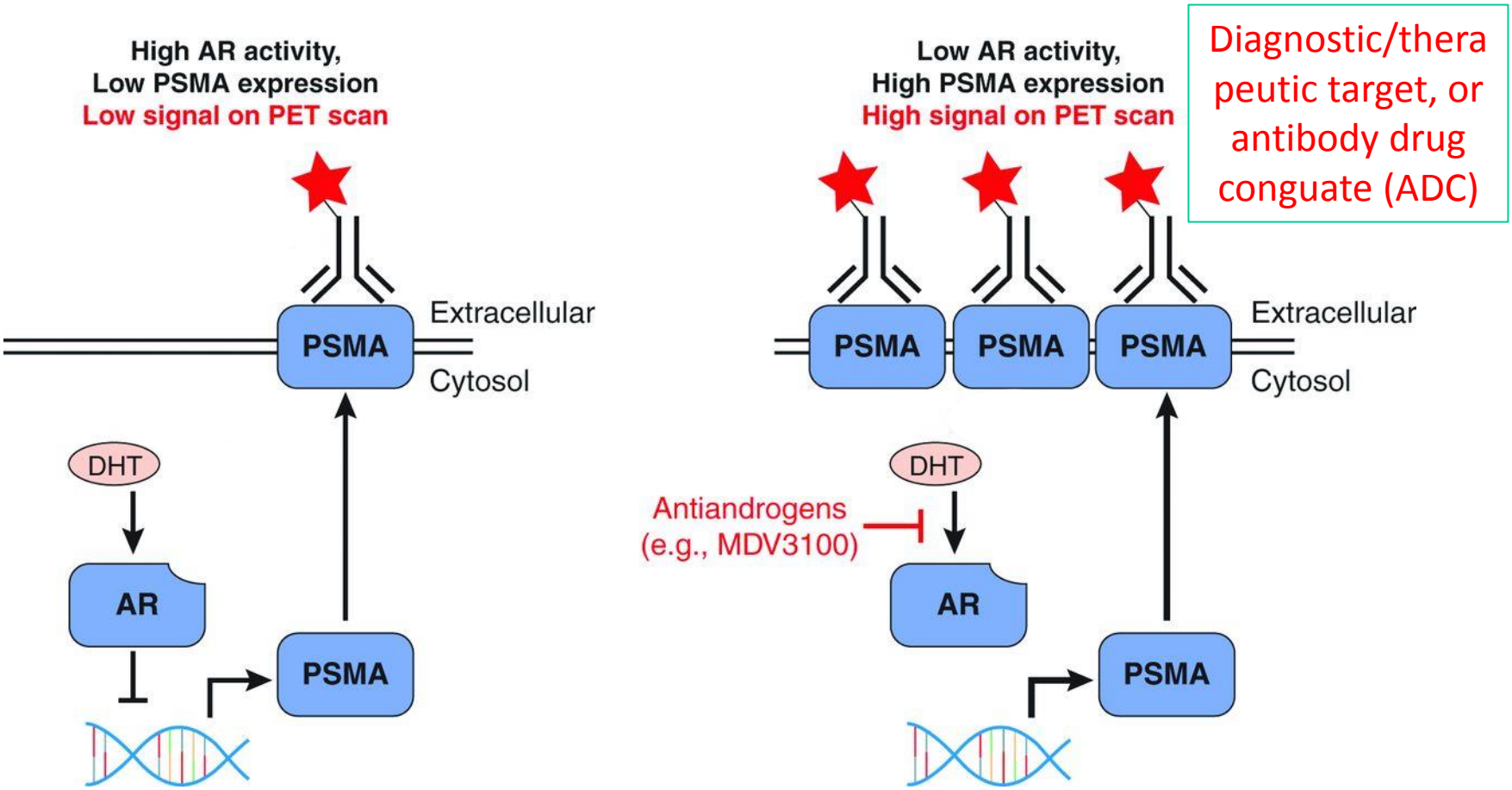
64 yo post prostatectomy. Rising PSA (2.3 ng/ml).

Ga/F-PSMA vs F/C-Choline PET/CT

- PSMA - transmembrane protein over-expressed in PCa
  - Not secreted (unlike PSA) - ideal extracellular target
- Higher sensitivity than FCH in liver and bone disease due to lower background uptake*
- Improved detection of local relapse and metastases in BCR than FCH*
- Better sensitivity than FCH at very low PSA levels (<0.5 ng/ml) however PSA dependence remains**

*Morigi JJ, et al. J Nucl Med. 2015; 56:1185-90
**Afshar-Oromieh A, et al. Eur J Nucl Med Mol Imaging. 2015; 42:197-209
**Eiber M, et al. J Nucl Med. 2015; 56:668-74

Noninvasively measuring AR signaling pathway output with a radiotracer targeting PSMA. A schematic representation of the relationship between AR activity and PSMA expression and the strategy to exploit this relationship for PET imaging.



Michael J. Evans Cancer Discovery 2012;2:985-994

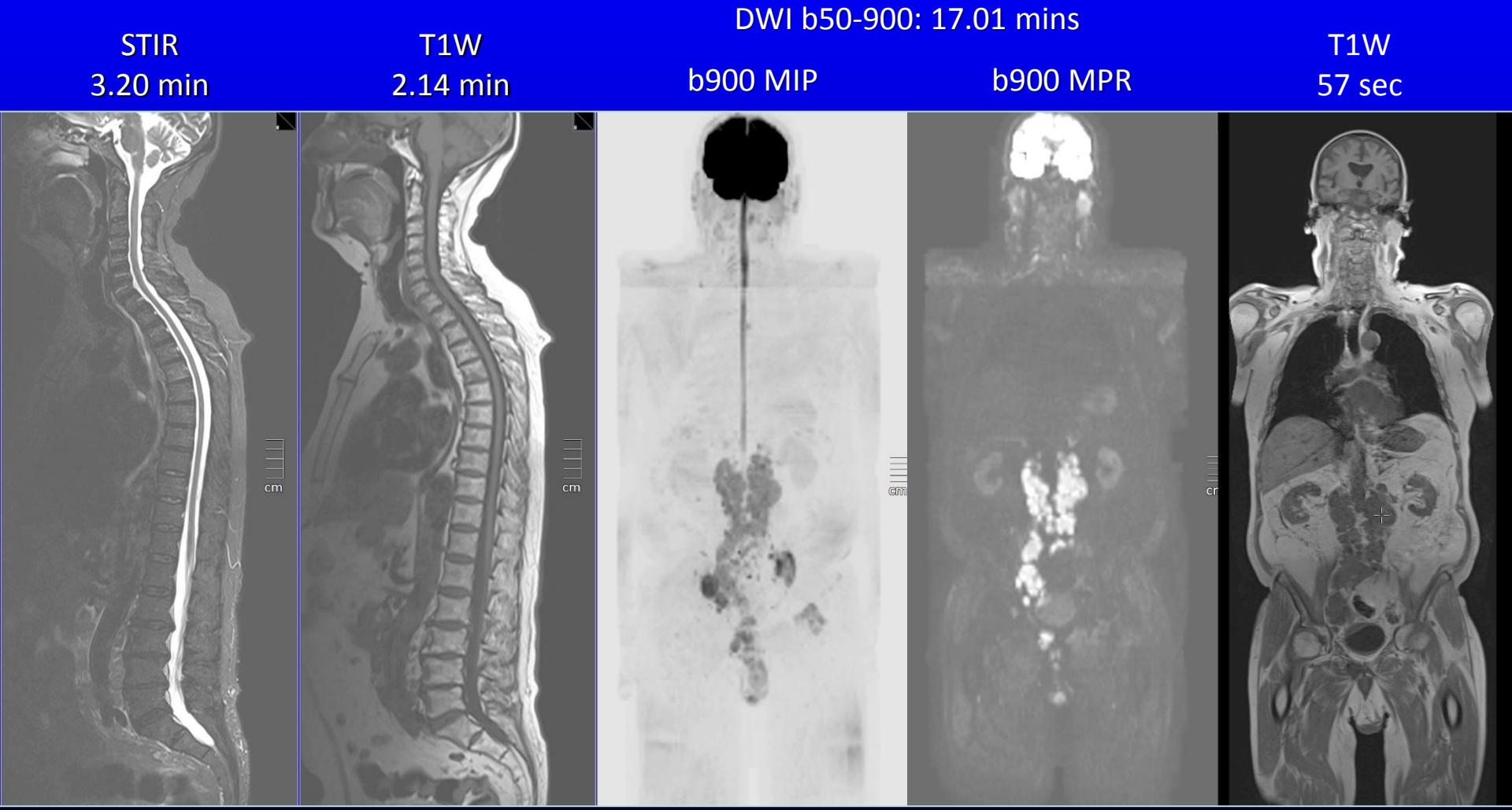
AACR American Association for Cancer Research
CANCER DISCOVERY

MRI: weighting towards bone constituents

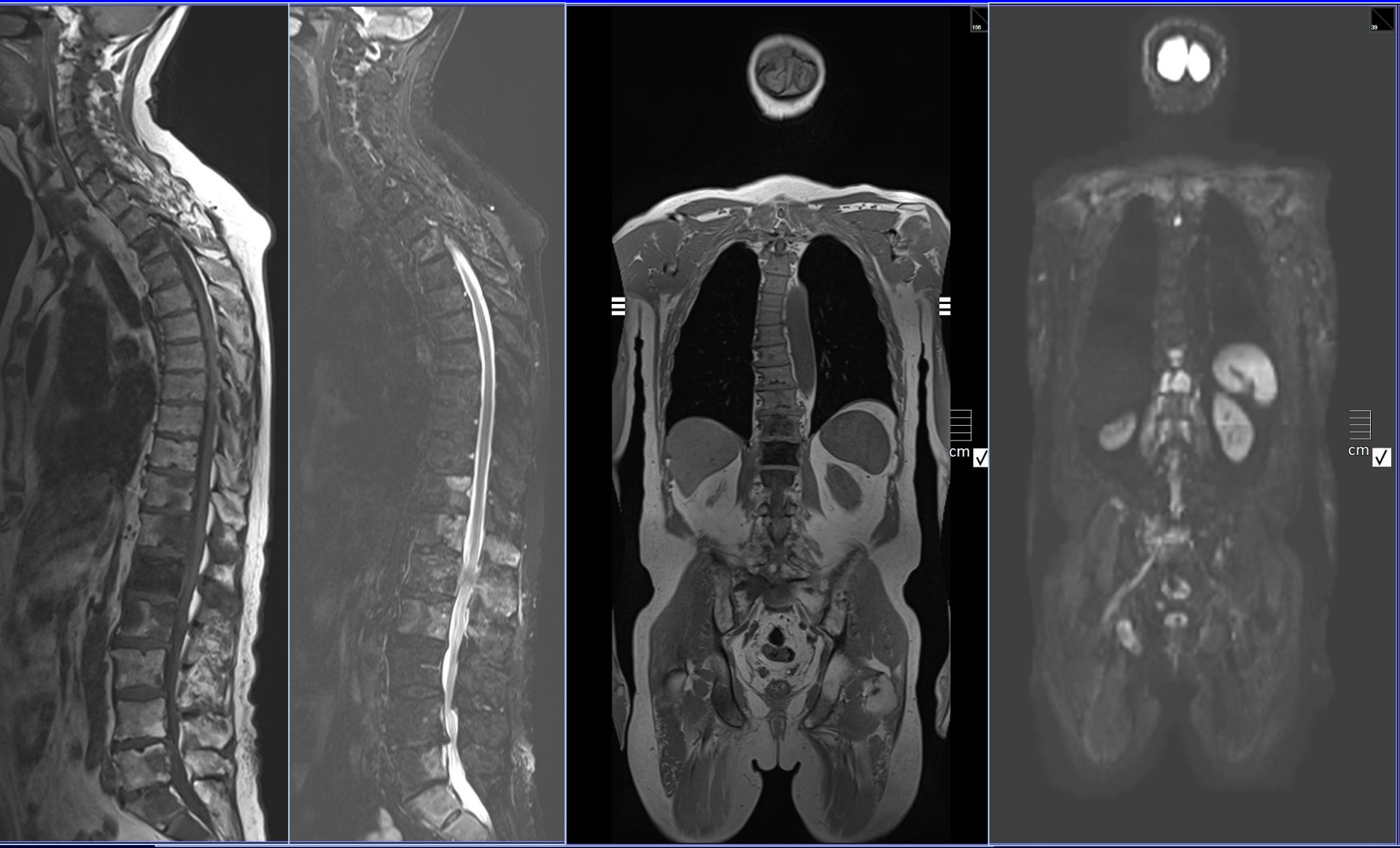
- T1-weighted spin-echo, T2-weighted (FS) & STIR
  - Cellular and water content
- Gradient recalled echo (Dixon)
  - Fat:water ratio and susceptibility induced by trabecular bone
- Dynamic contrast enhanced (DCE) MRI
  - Vascularisation
- Ultrashort TE (UTE)
  - Trabecular bone structure & density
- DW-MRI
  - Cell density, fat and water content

The ability to use multiple techniques in a single examination makes MRI truly multimodal

Bone only assessments are achievable in =30 mins; Bones & soft tissues ≈ 45 mins

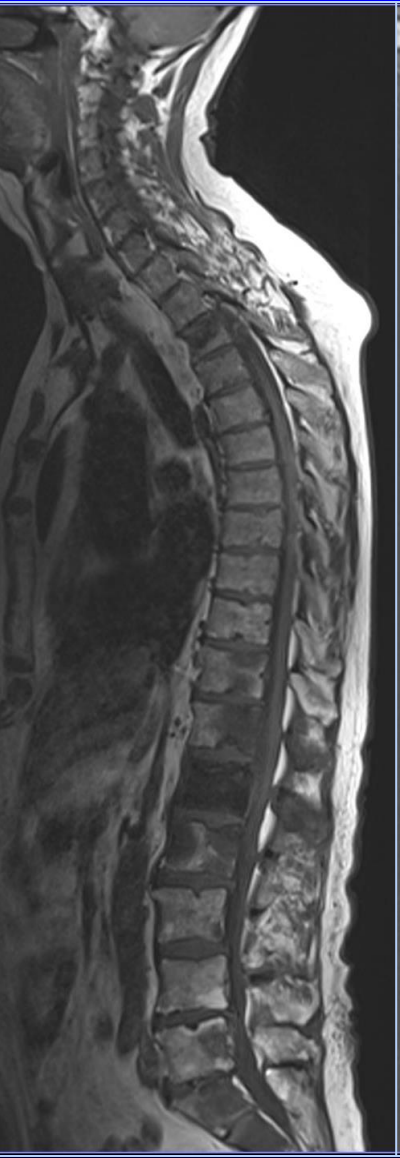
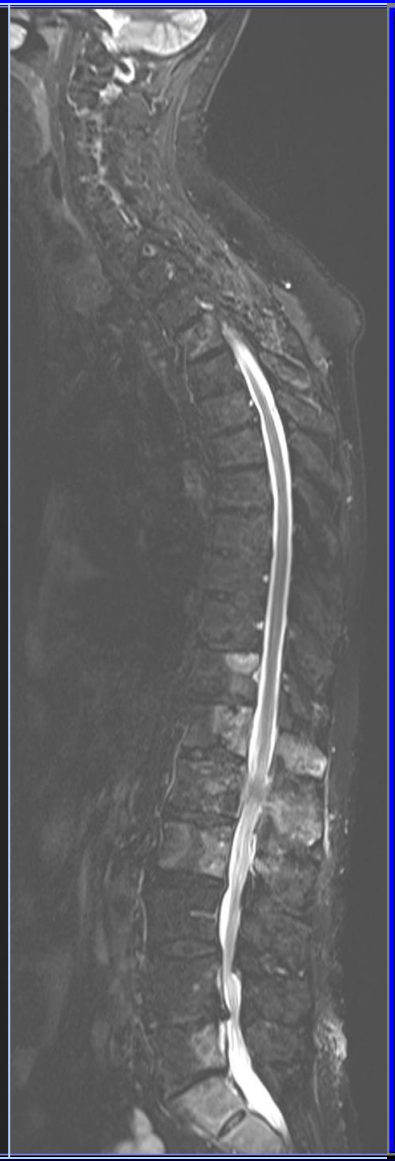
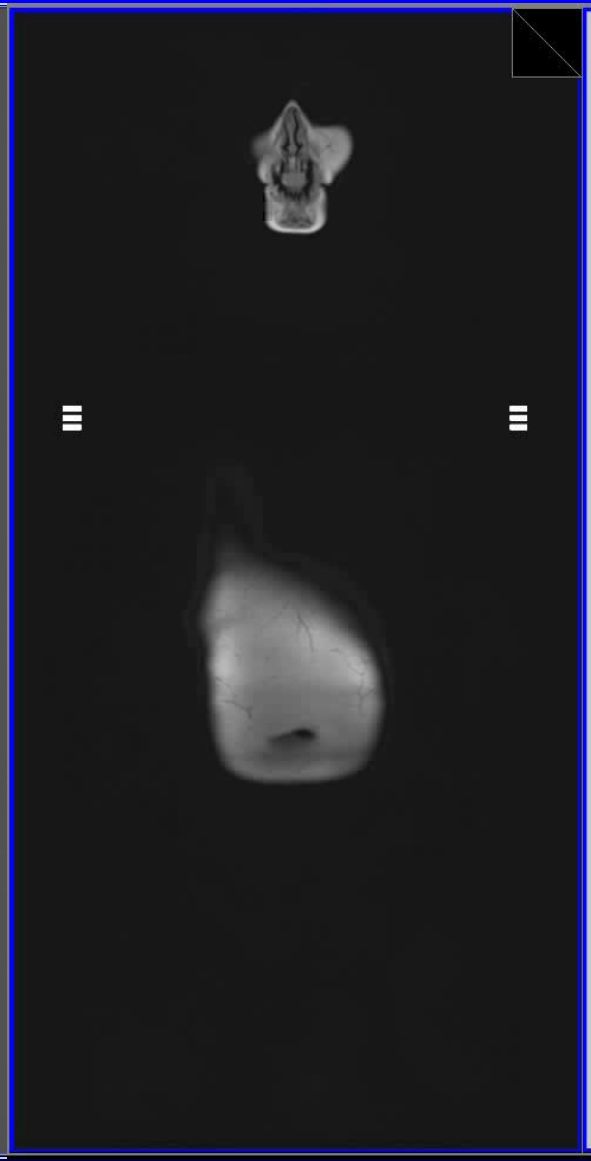
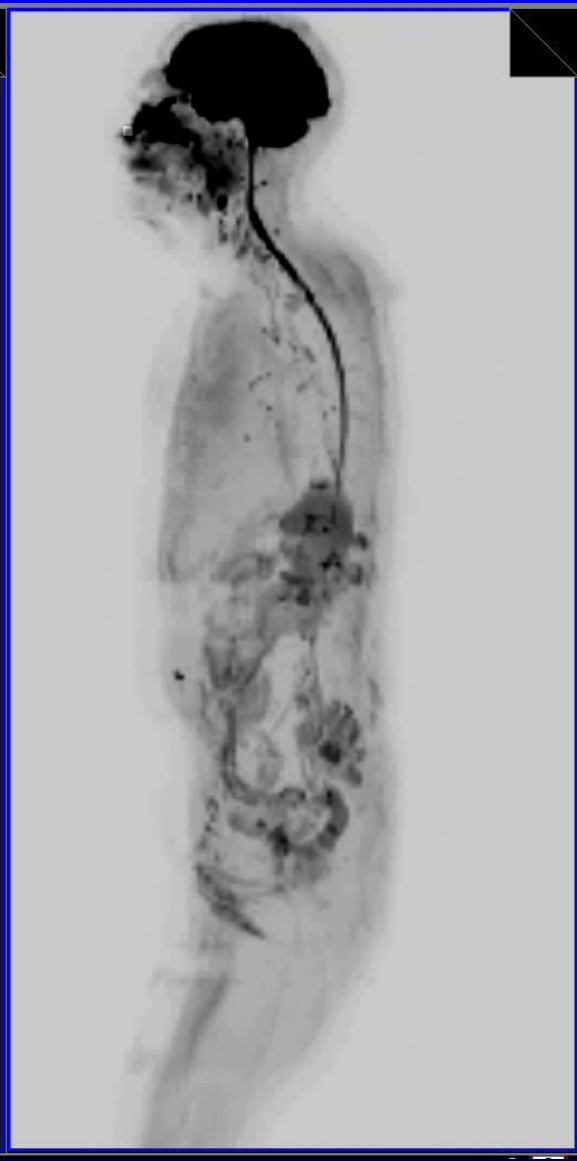


T1W T2W+FS T1W b900



73 male. mCRPC. Asymptomatic. Rising PSA (45.7ng/mL) on Abiraterone. Restaging.

T1W T2W+FS T1W b900-MIP

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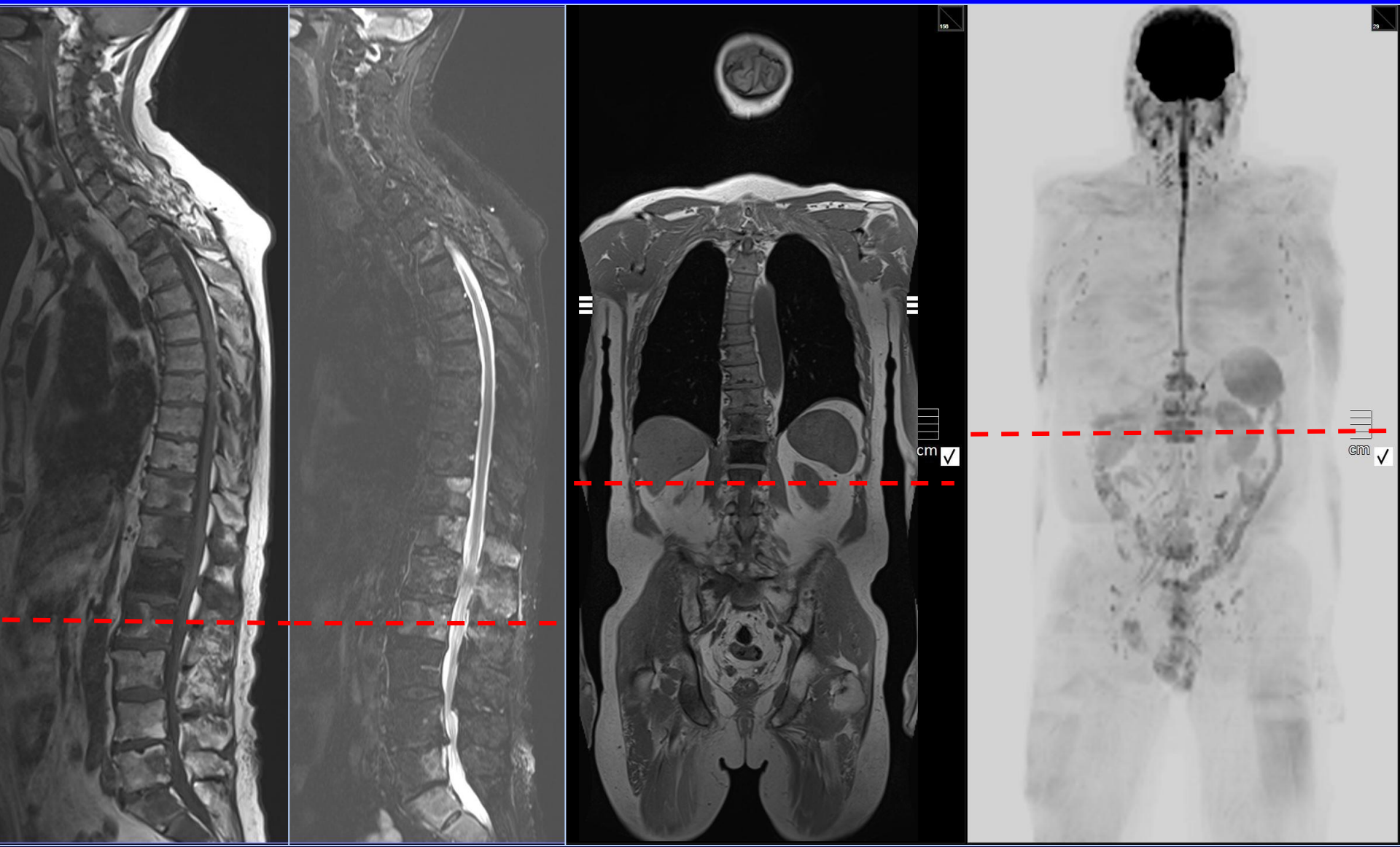
T1W T2W+FS T1W b900-MIP



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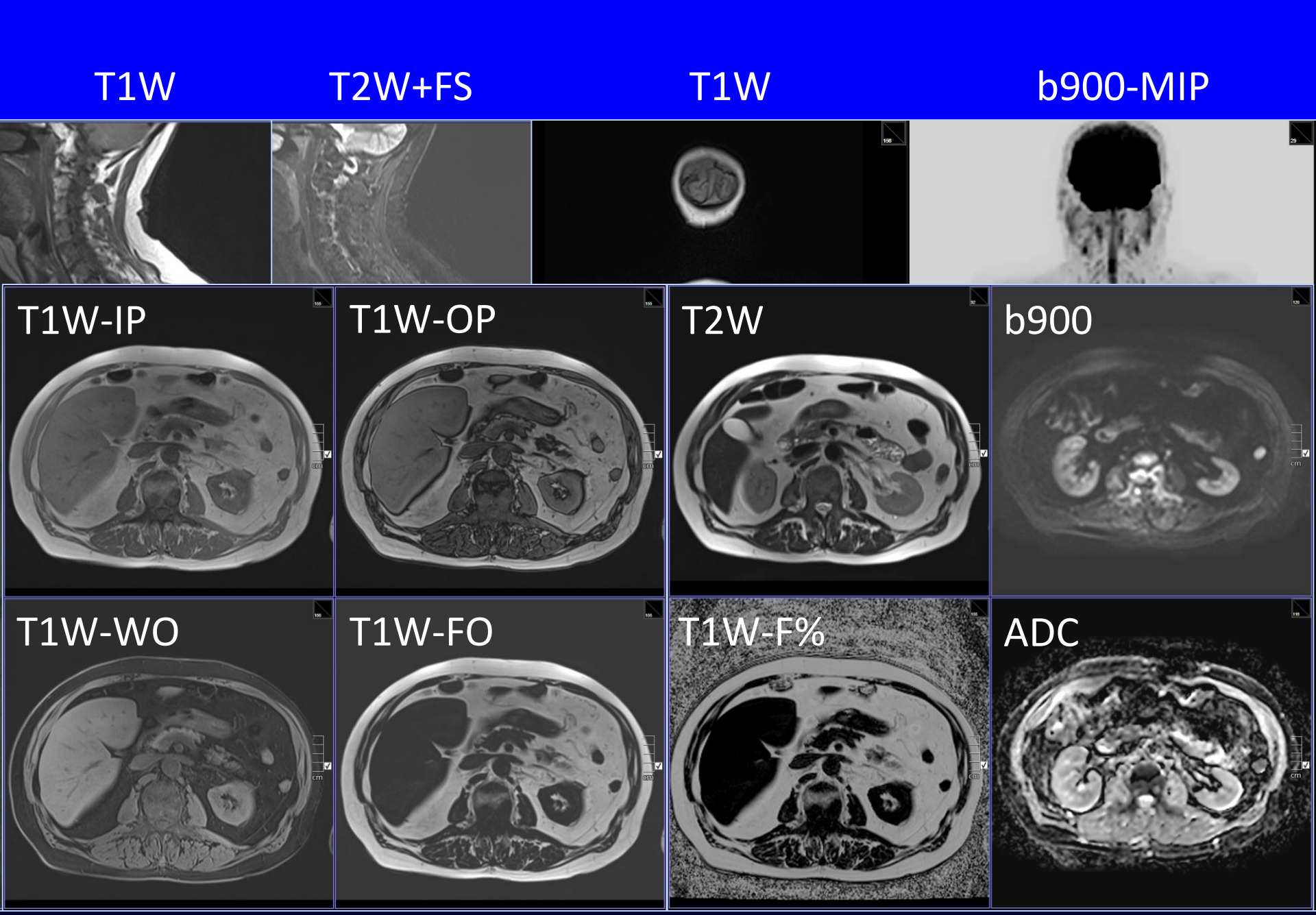
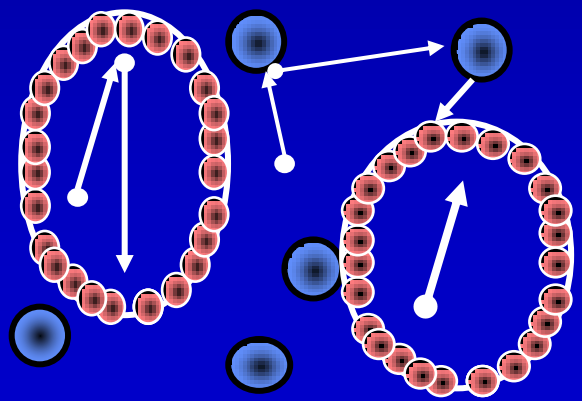


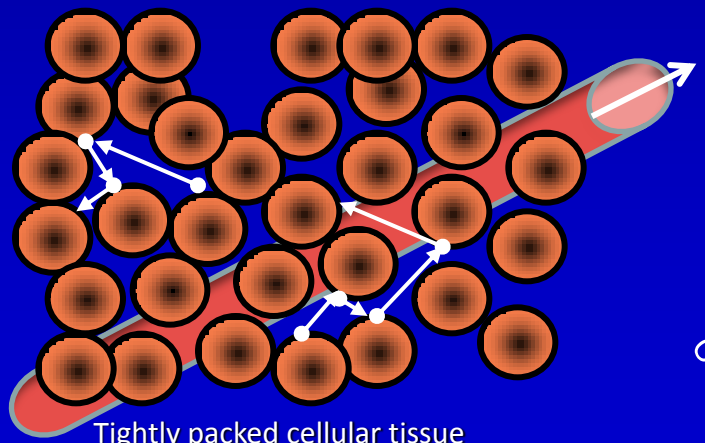
73 male. mCRPC. Asymptomatic. Rising PSA (45.7ng/mL) on Abiraterone. Restaging.

Diffusion MRI – evaluates microstructure

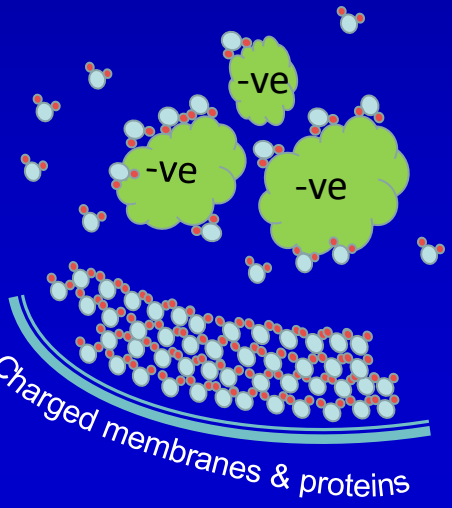
- Evaluates microscopic motion of water in tissues (nm-µm scale)
- Reflects tissue architectural properties including vessels/ducts, extracellular space tortuosity & intracellular complexity
  - Perfusion, cellular arrangements, cell size distributions & cellular density, extracellular space viscosity, glandular structures, integrity of membranes, nuclear-cytoplasmic ratio & the unique interconnected "social" properties of intracellular water
- ADC ($x10^{-3}$ mm^2/s; $\mu m^2/s$): net impeded water diffusivity of tissues



Organised glandular tissue, cysts, haemangioma, pancreas

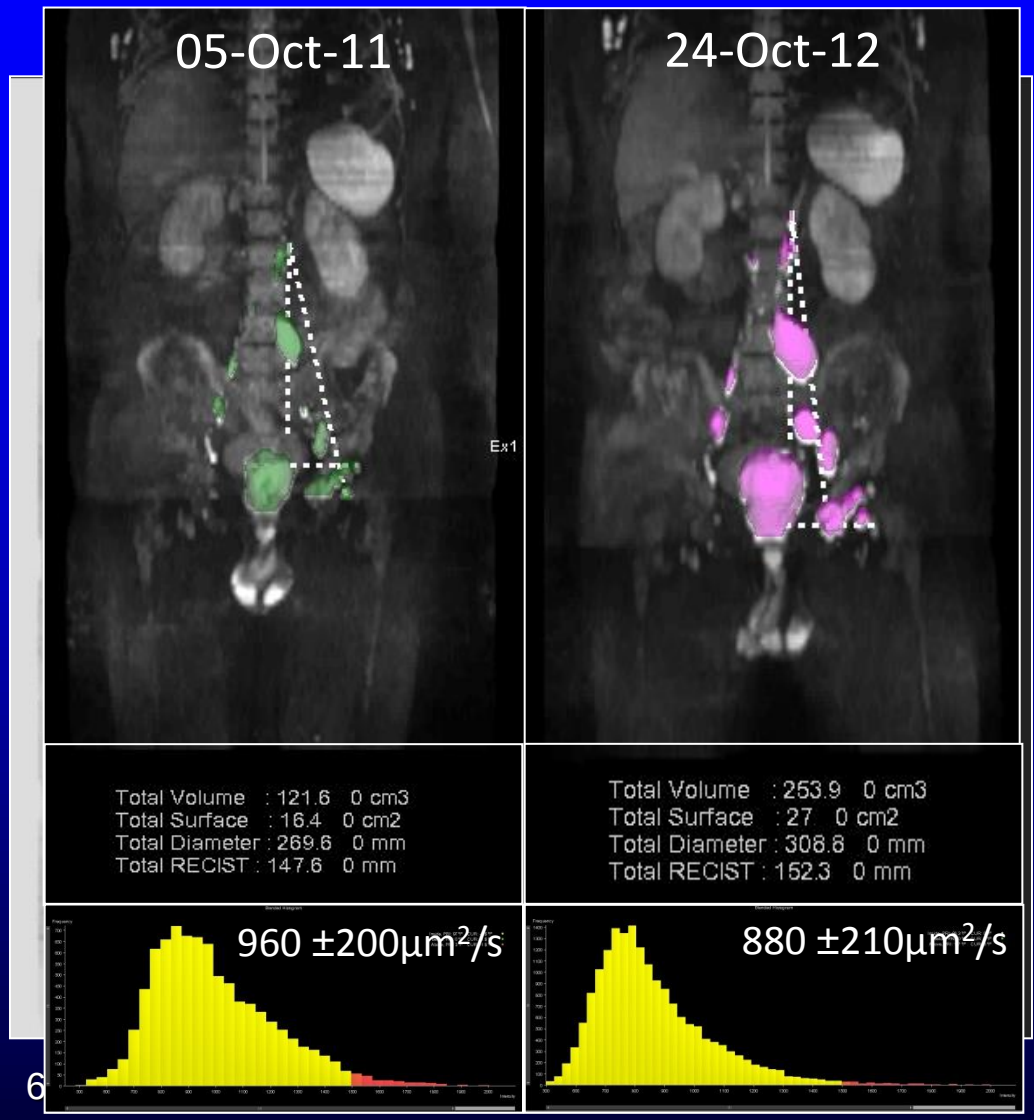


Tightly packed cellular tissue
Blood vessels



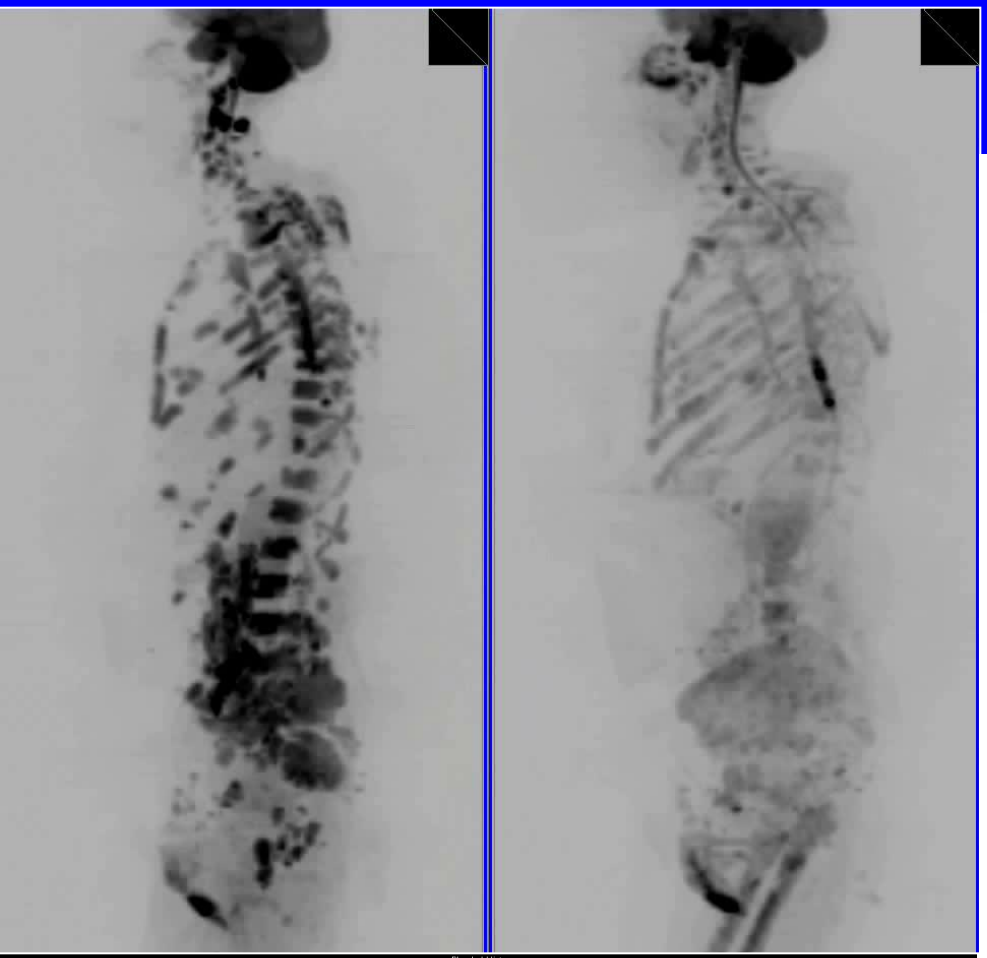
Whole body DWI for metastasis detection

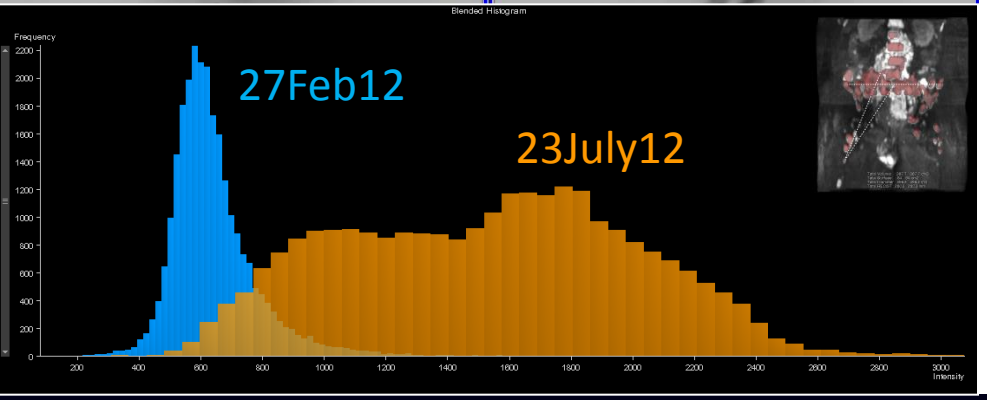
- Widespread availability
- Better than CT scans and bone scans for lytic bony disease
- Soft tissue assessments: primary, nodal & liver
- Advantages
  - 3 dimensional & whole body
  - Economically viable
  - No radiation. No injections of isotopes or contrast medium
  - Quick to perform & read
  - Repeatable
  - Quantitative (volume/ADC)



Padhani AR, Koh DM, Collins DJ. Whole-body diffusion-weighted MRI in cancer: current status and research directions. Radiology 2011; 261(3):700-18

27Feb12 23July12

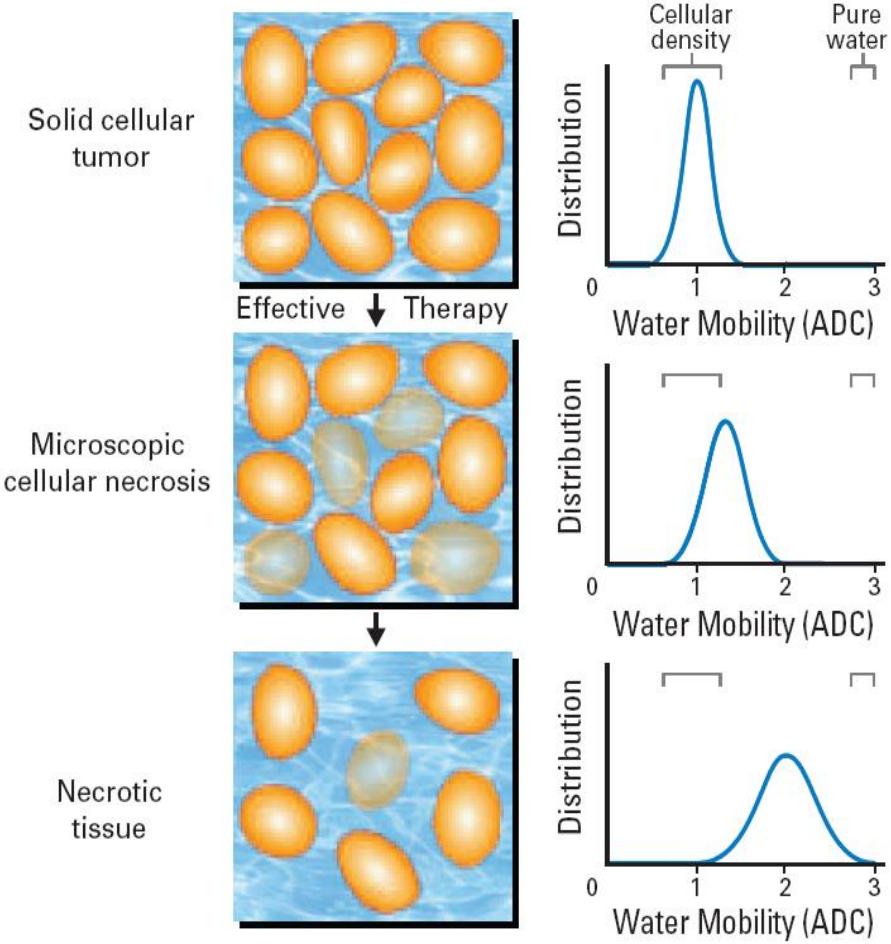




Prostate Cancer

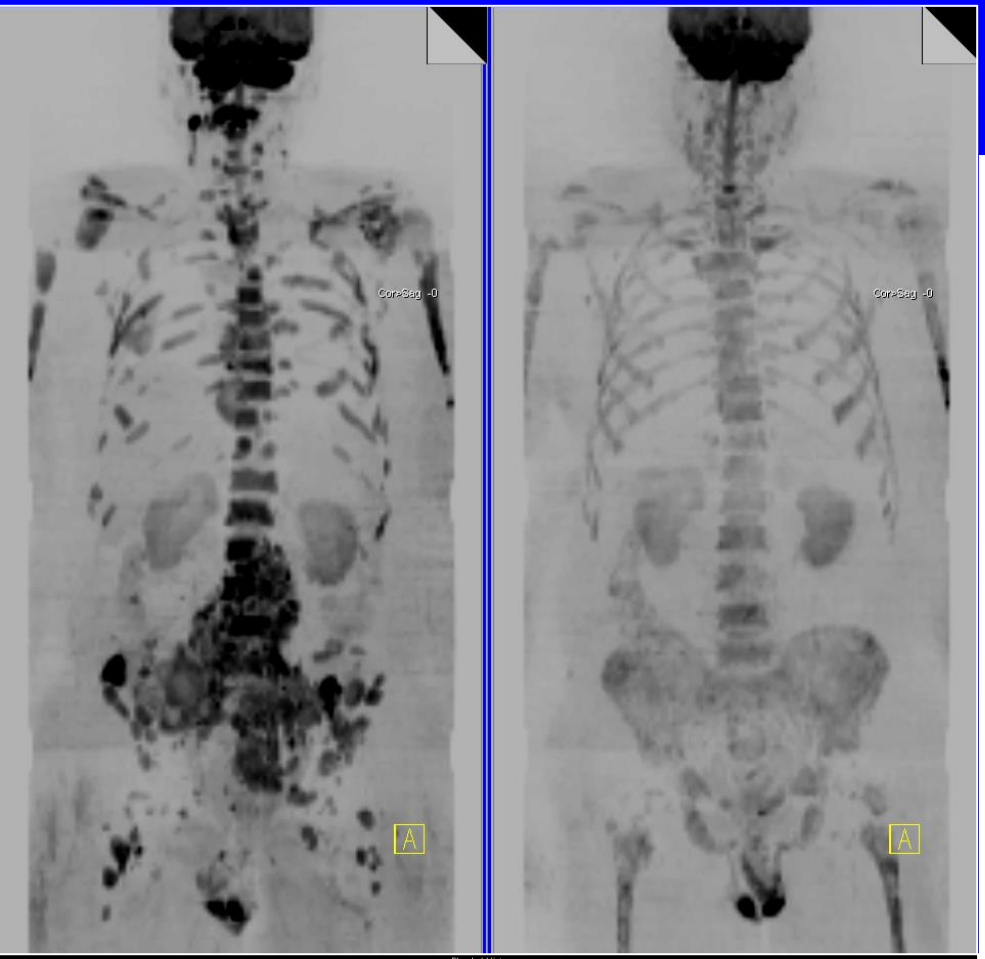
Rx: x4 docetaxel+prednisone

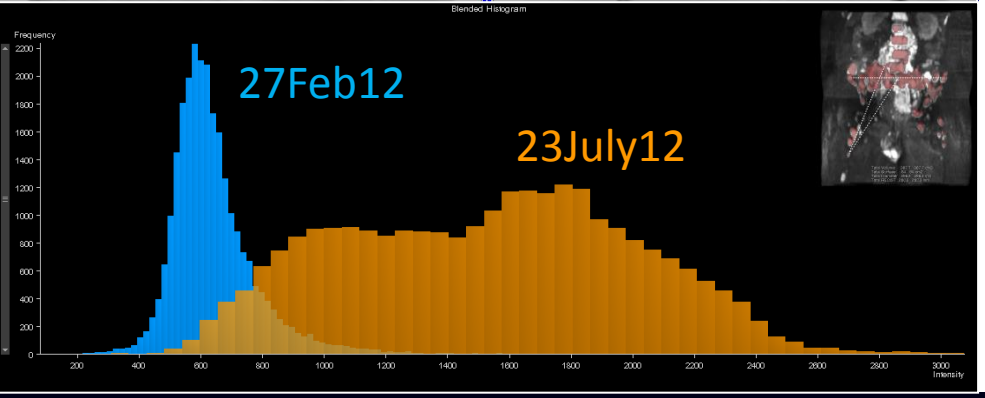
Biological processes involved in therapy induced changes in DWI



Hamstra DA, et al, J Clin Oncol 2007: 25:4104-4109

27Feb12 23July12





Prostate Cancer

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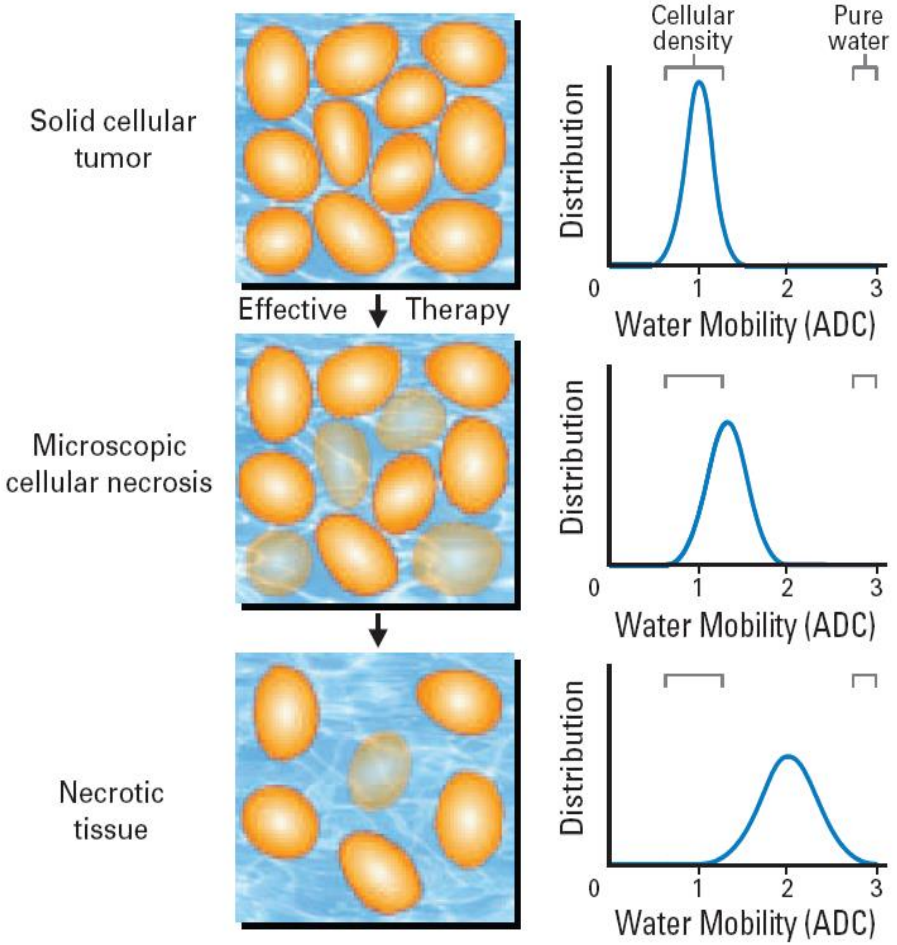
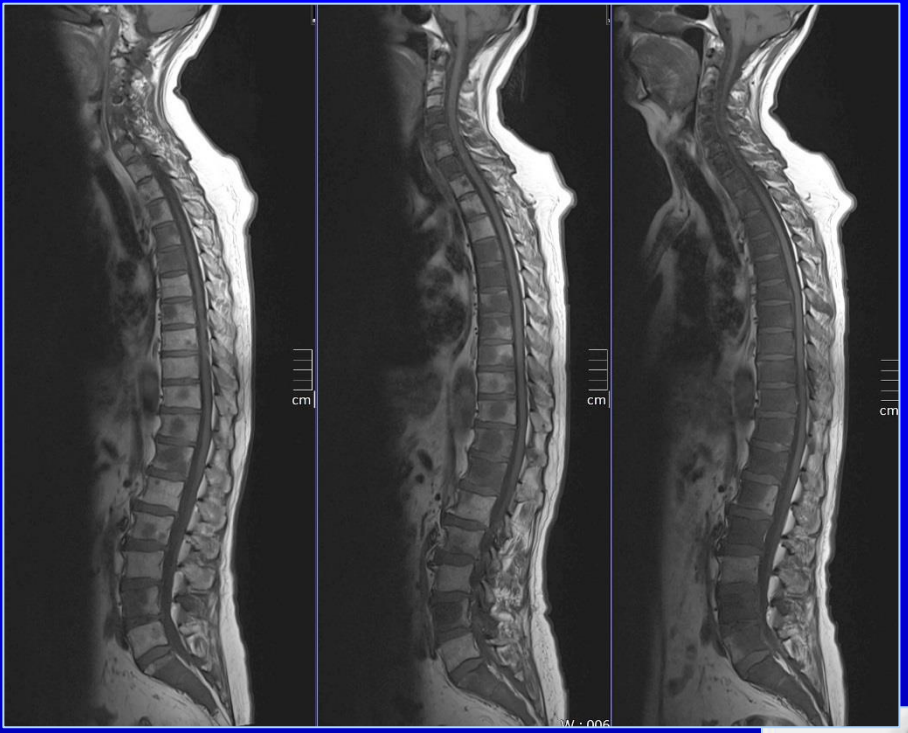


Hamstra DA, et al, J Clin Oncol 2007: 25:4104-4109

Radium-223 50kBq/kg every 28 days (Baseline, 1 cycle and 3 cycles)



24Aug15
216 ng/ml

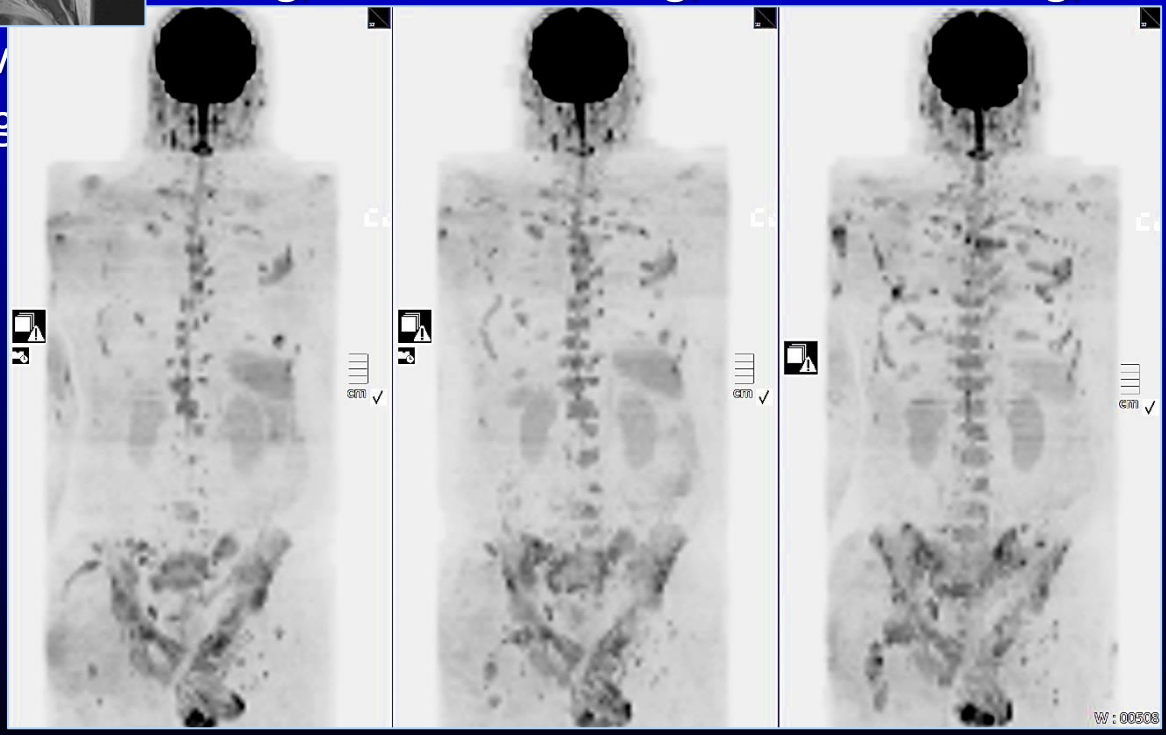
22Sept15
237 ng/ml

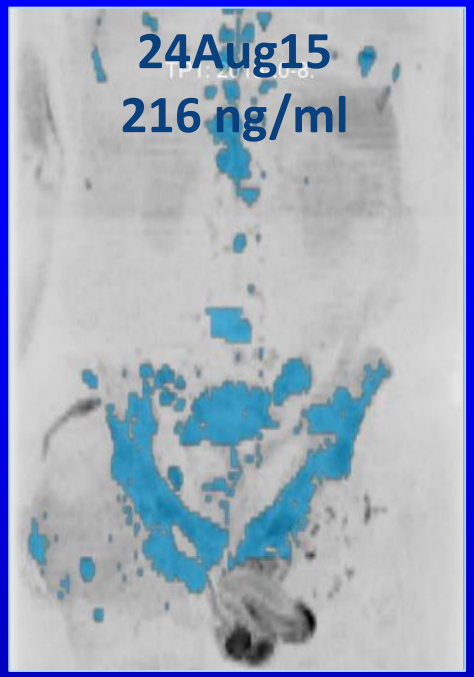
23Nov
320 ng

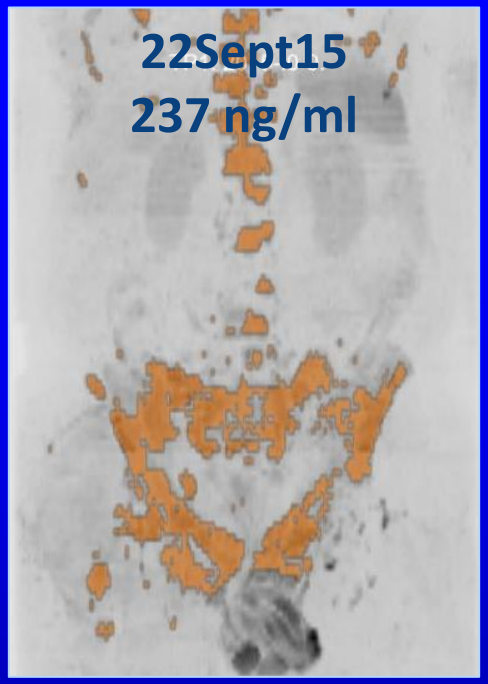
24Aug15
216 ng/ml

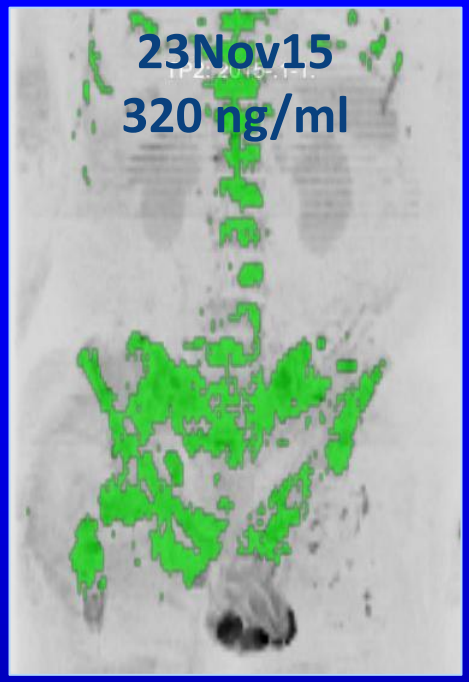
22Sept15
237 ng/ml

23Nov15
320 ng/ml

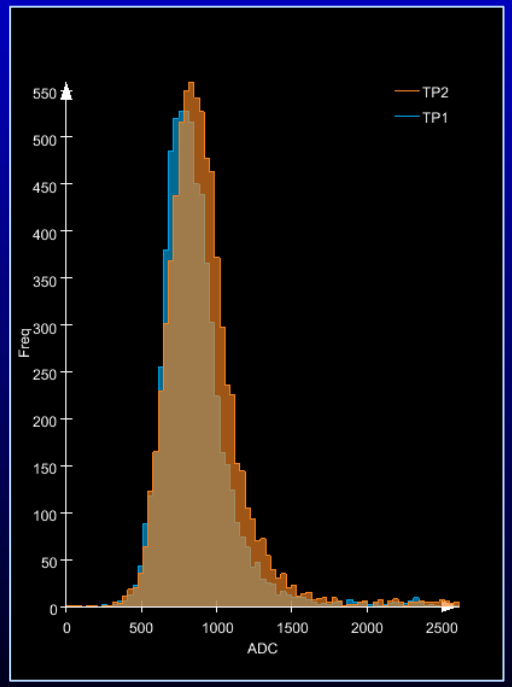


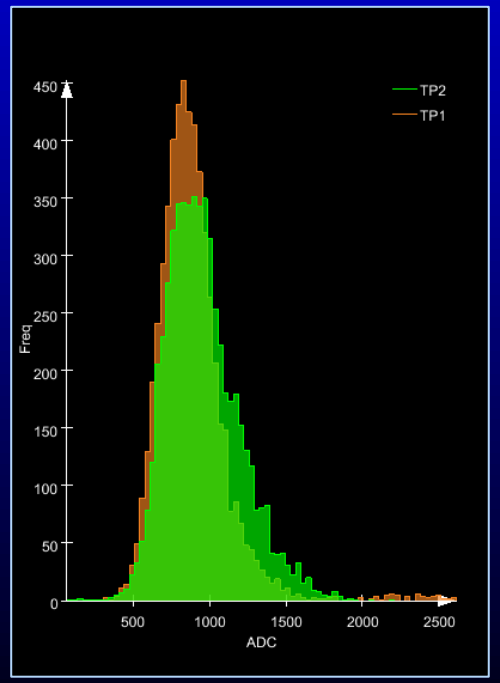




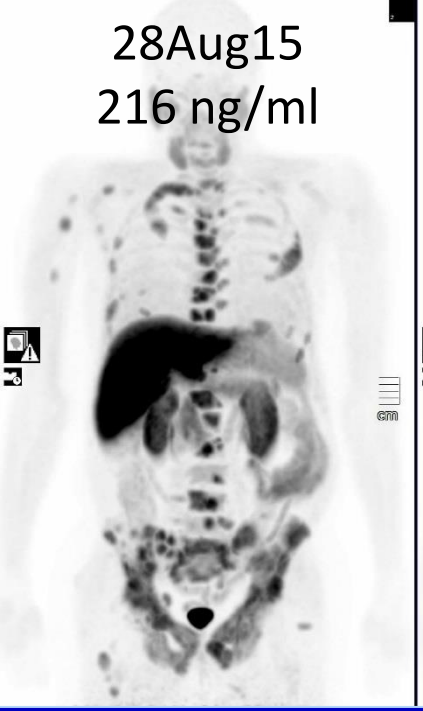


Siemens whole body tumor load software – WIP (not for clinical use)

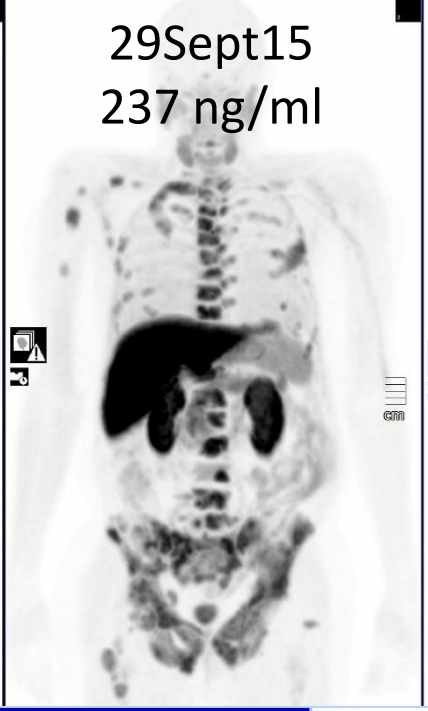




28Aug15
216 ng/ml



29Sept15
237 ng/ml



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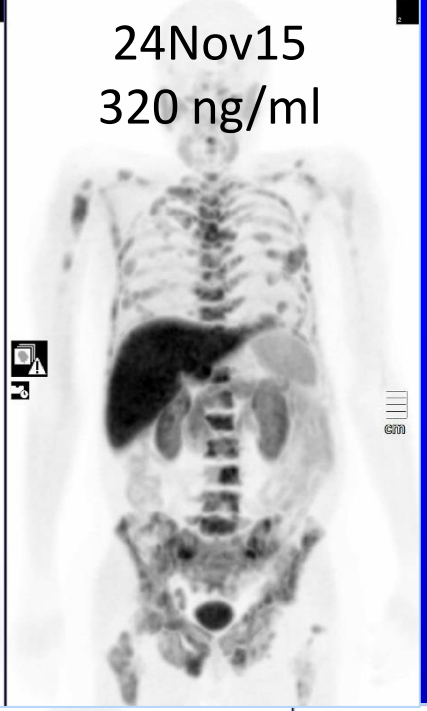
320 ng/ml

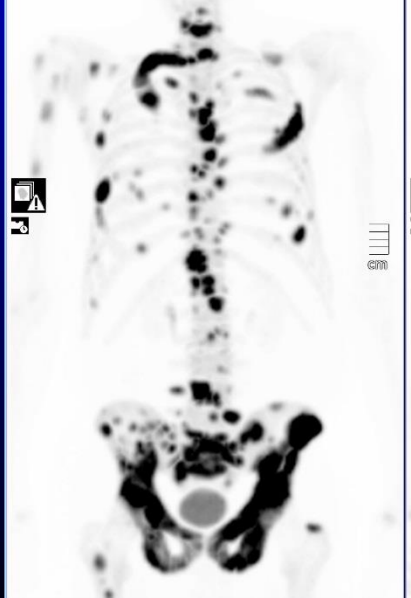


FCH PET/CT

Radium-223
50kBq/kg every 28 days (baseline, 1 cycle and 3 cycles)

NaF PET/CT

25Aug15
216 ng/ml



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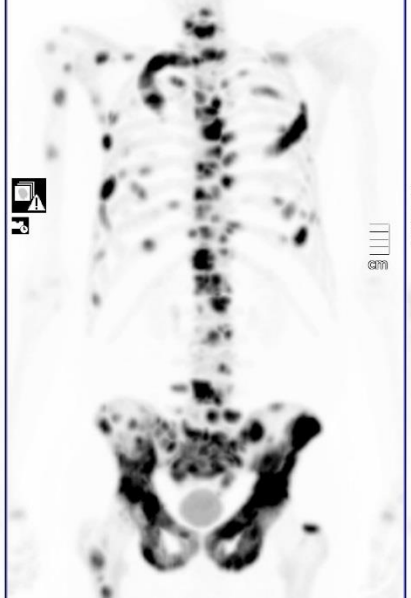
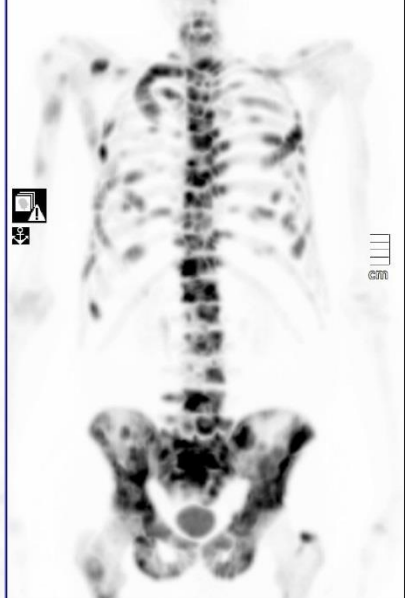


26Nov15
320 ng/ml

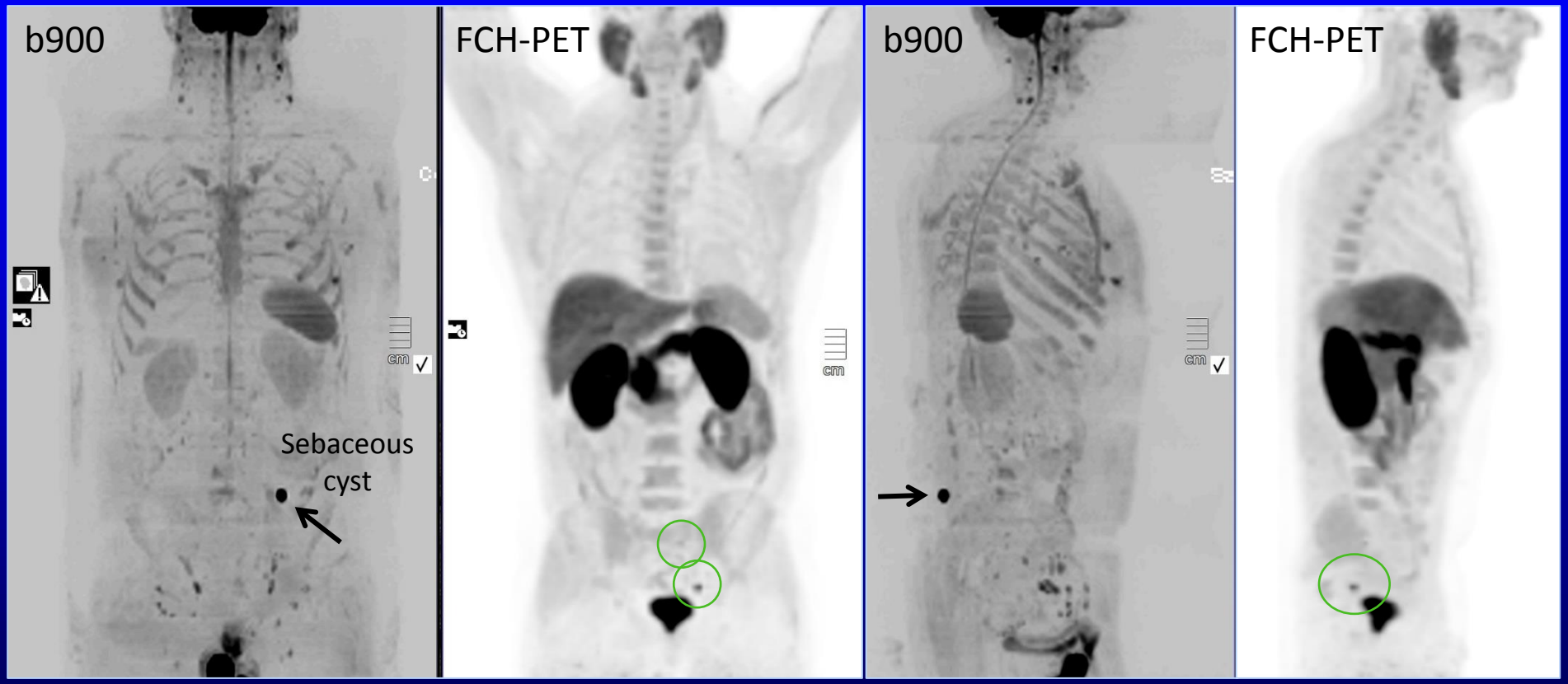


Which imaging tests for clinical practice for metastasis detection?

- Planar Tc-99m BS do NOT provide robust evidence for ruling-in/ruling out early M+ (SPECT-CT improves specificity)
- A sensitive, single modality method for detecting bone and nodal disease is preferable to separate examinations
  - WB-MRI could replaced CT + bone scan to confirm M0; identify early M+ disease (evidence base is incomplete)*
  - 18F-choline and/or 18F-NaF PET/CT could be an effective combination**
    - *Used when WB-MRI is negative & clinical suspicion remains high*

*Lecouvet, F et al. Can Whole-body MRI with diffusion-weighted imaging replace Tc 99m bone scanning and computed tomography for single-step detection of metastases in patients with high-risk prostate cancer? Euro Urol 2012; 62:68-75
**Wondergem M, et al. A literature review of 18F-fluoride PET/CT and 18F-choline or 11C-choline PET/CT for detection of bone metastases in patients with prostate cancer. Nucl Med Commun. 2013 Oct;34(10):935-45.

FCH PET/CT better at detecting microscopic nodal disease



08-12-14 15-12-14 08-12-14 15-12-14

66M Post prostatectomy for pT3a, Gl 4+3 tumor & post-operative pelvic RT. PSA increasing 1.6 ng/mL. Rx SBRT.

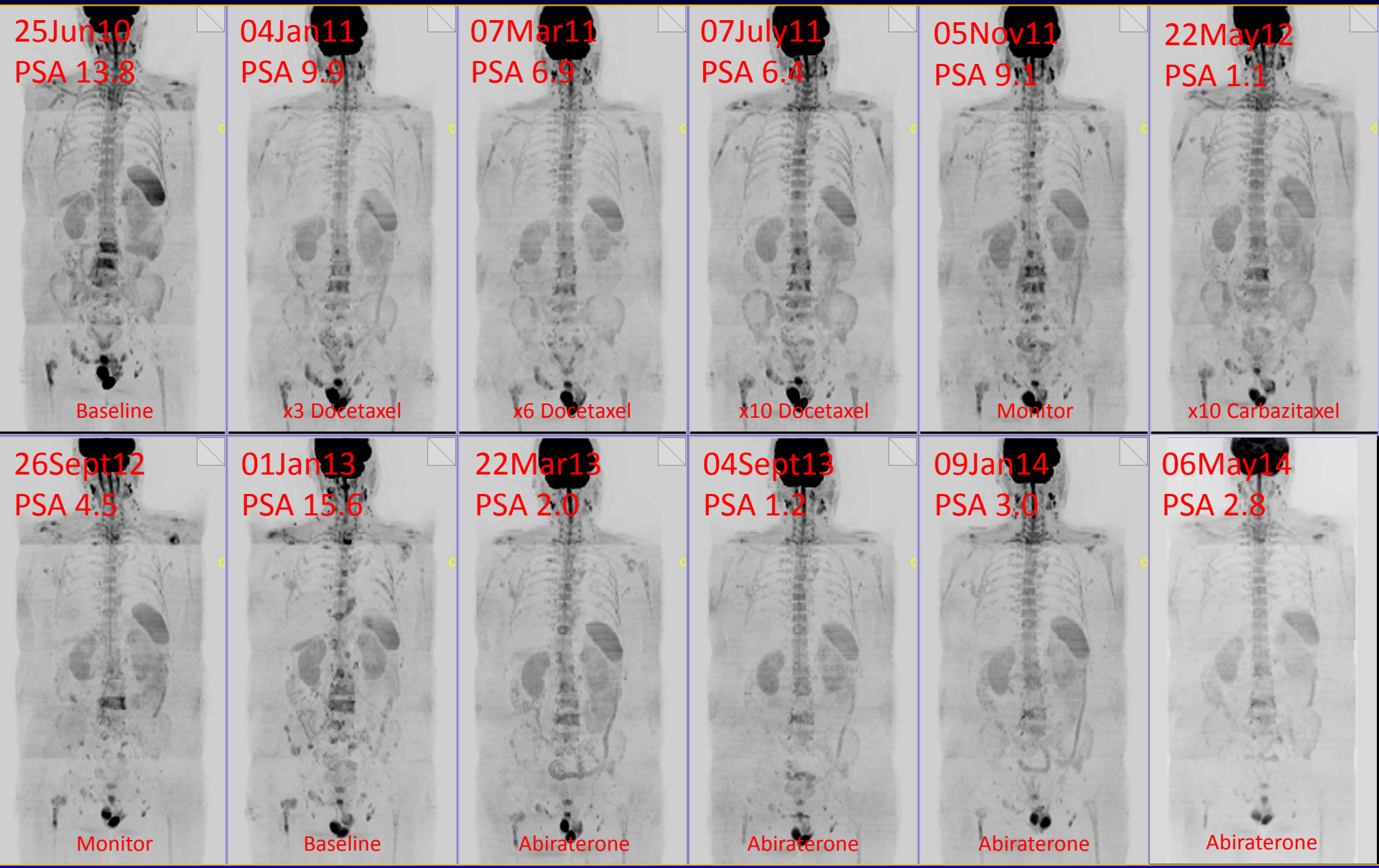
2015: Which imaging tests for clinical practice for response assessments?

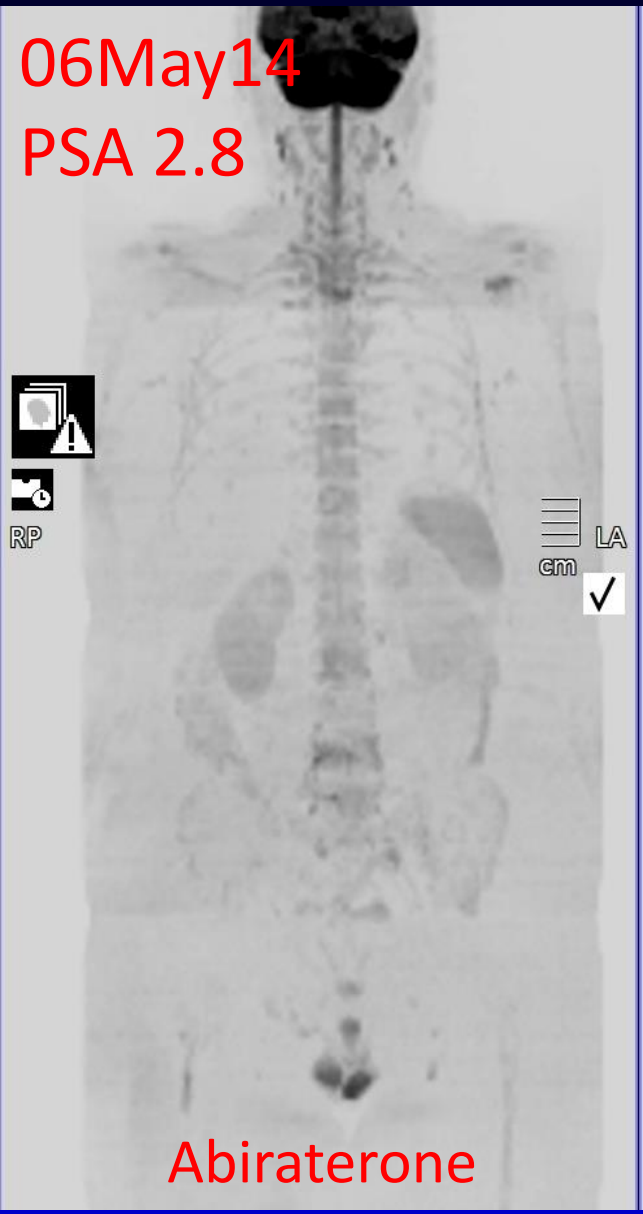
- Stop using pain as the primary progression criterion (PROs) in asymptomatic or minimally symptomatic patients*
  - Minimizes undiagnosed disease progression; ± patient harms
  - Minimizes delays in patient journeys through Rx options when disease burdens are lower (possible DFS/OS benefits)
- Imaging should be used to assess therapy benefits by directly evaluating tumor viability (Rx to maximal response)
  - BS/CT radiologic PFS should be for clinical trials**; not for practise
  - WB-MRI is the preferred imaging technique (FCH-PET alternative)
  - Even MRI has problems including evaluating disease activity on the background of scarring (previous therapies) & sclerotic progression

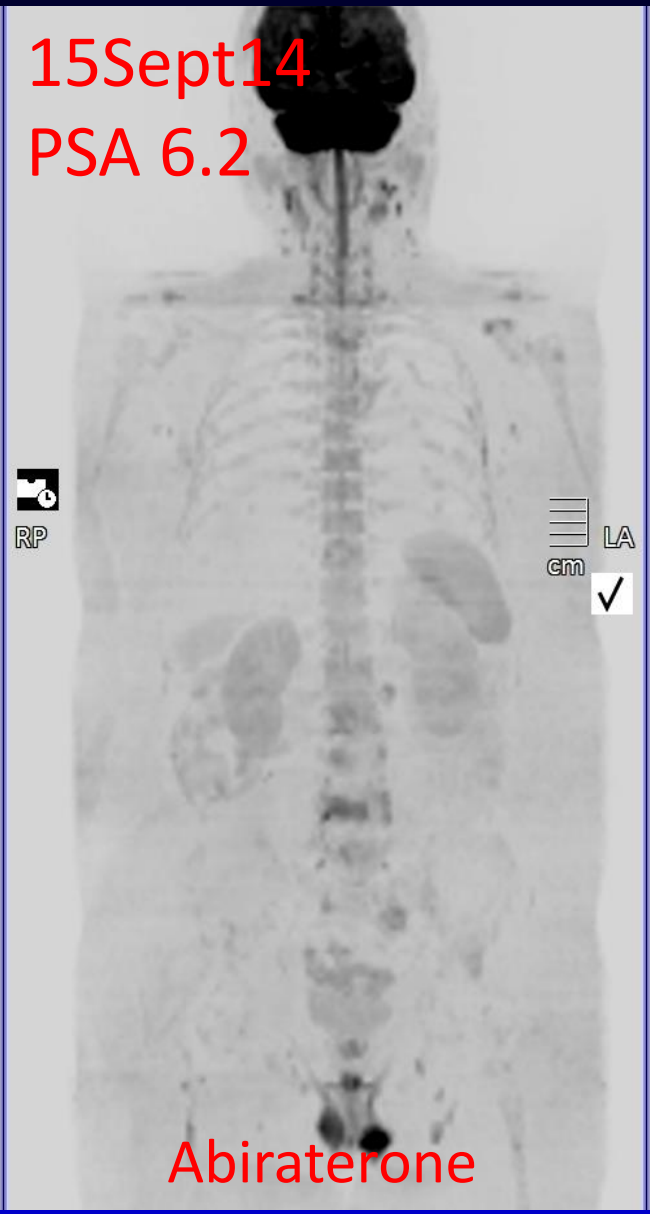
*Morris MJ, et al. Semin Oncol. 2013 Jun;40(3):375-92.
** Morris MJ, et al. J Clin Oncol. 2015 Jan 26. [Epub ahead of print]

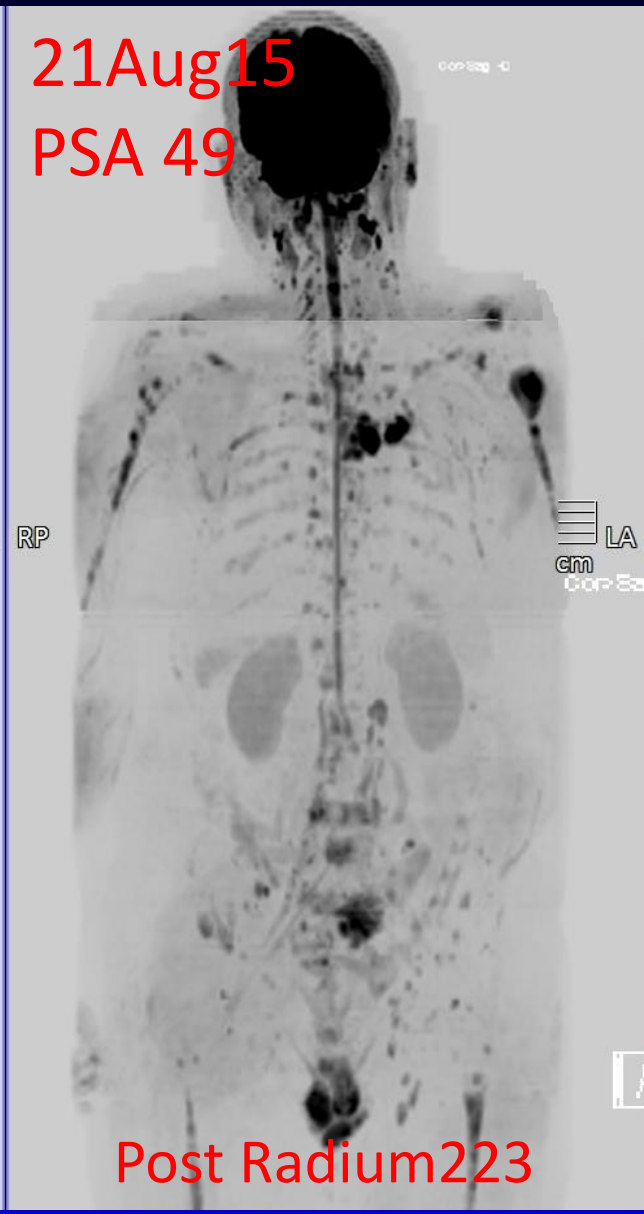
Asymptomatic disease

Using WB-MRI to titrate Rx in PSA oligo-secretory disease




06May14
PSA 2.8
RP
LA
cm
Abiraterone


15Sept14
PSA 6.2
RP
LA
cm
Abiraterone


21Aug15
PSA 49
RP
LA
cm
Post Radium223

Composite measures of response are needed for metastatic APC assessments in 2015

Chemotherapy	Endocrine	Immunotherapy	Radiopharmaceuticals	Others in class (platinum)/other classes (PARP inhibitors/cabozantinib prednisone/combinations
Docetaxel Carbizitaxel	Abiraterone Enzalutamide	Sipuleucel-T	Alpharadin	
Denosumab & Zoledronic acid				

Current/old evaluation of response

Symptoms/PSA/bone scan/CT scans/SRE/SSE

Soft tissue disease			Bone disease (sole site in 70%)	
Resp-onse (needs confirmation)	Stable	Progression	No progression	Progression (delayed: needs confirmation)

Modern predictors/measures of response

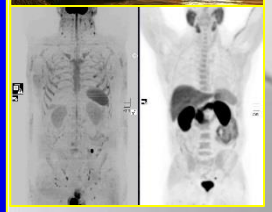
Multimodal imaging/ Hb, LDH, ALP, albumin/ ±PSA/±CTCs ±AR-V7

Soft tissue disease			Bone disease (sole site in 70%)		
Resp-onse	Stable	Progression	Response	Stable	Progression

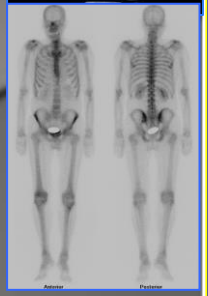
Oncologists' thinking regarding Rx with novel MOA

Patient care ± economic impacts

	CT	WB-MRI	BS	PET -CT Bone specific tracers	PET Choline, PSMA, FDHT
Strengths	Widely available Low cost Fast acquisition Soft tissue and lytic bone metastases – detection and response assessment	Lack of radiation or need for cyclotron High spatial resolution Versatile & multiparametric ADC = quantitative, highly reproducible imaging response biomarker Lower cost than PET-CT	Widely available and accepted Low cost Used as part of PCWG criteria	High sensitivity and relatively good specificity for bone metastases	Emerging data with relatively good sensitivity and specificity in detection of 1st relapse and in metastatic patients
Weakness	Non-lytic bone metastases detection or response assessment Subcentimetre nodes classification Poor local disease delineation Radiation	Scanner dependent 45-60 min acquisition time Susceptible to artefacts Reduced performance in subcentimetre nodal and lung metastases Influenced by treatments (GCSF)	210-240 min acquisition time Depict bone only disease Poor specificity Low sensitivity No response criteria FLARE phenomenon Radiation	120-180 min acquisition time Needs cyclotron Depict bone only disease No response criteria Presence of FLARE of bone metastases with therapy Radiation High cost	120-180 min acquisition time Needs cyclotron Reduced performance in subcentimetre nodes Performance not well known in the presence of ADT Radiation High cost
Opportu-nities	Complementary to PET or MRI acquisition - Sclerotic response - Lung metastases - Lytic vs non-lytic bone metastases classification	Radiation free long term follow-up Surgical planning for local disease Skeletal events detection (MSCC, fractures) “One stop shop” - metastatic bone and soft tissue imaging response criteria	Bone scan index – prognostic Improved performance with SPECT-CT	SUV – potential response biomarker	Molecular subset patients classification Improved detection of early relapse and accuracy in detection oligometastattic disease
Threats	Competing MRI and PET technology	Lack of standardization and widely available expertise Lack of established response criteria in metastatic bone disease	Poor performance Competing PET technology	Lack of standardization and widely available expertise Lack of established response criteria in metastatic bone disease	Lack of standardization and widely available expertise Lack of established response criteria in metastatic bone disease



When it doesn't feel right, go left



"The one who follows the crowd will usually go no further than the crowd...

...The one who walks alone is likely to find himself in places no one has ever been before" - Albert Einstein

Next steps for WB-MRI in APC

- Standardizing imaging: data acquisitions across a variety of machine types, proforma reporting and data collection*
- Precision estimates: Inter- and intra-observer variability and reproducibility assessments of qualitative and quantitative MRI assays (ADC values, tumour volume, bone tissue sub-classification, heterogeneity metrics)
- Clinical trials powered for imaging BM validation:
  - Detection studies: oligometastatic protocols, non-metastatic CRPC
  - Established and novel treatments: androgen axis inhibitors, chemotherapy, Radium223, immunotherapies, PARP inhibitors
  - Adaptive therapy studies for imaging depicted heterogeneous response

* Recommendations on whole body MRI for skeletal assessments of advanced prostate cancer. AR Padhani, F Lecouvet, N Tunariu, DM Koh, DJ Collins, F De Keyzer, HP Schlemmer, G Petralia, E Sala, B Tombal, J DeBono – in preparation