Parma, 19 maggio 2015

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma

PDTA tumore della prostata

Imaging molecolare e nuovi radiofarmaci: La PET e il Ra-223

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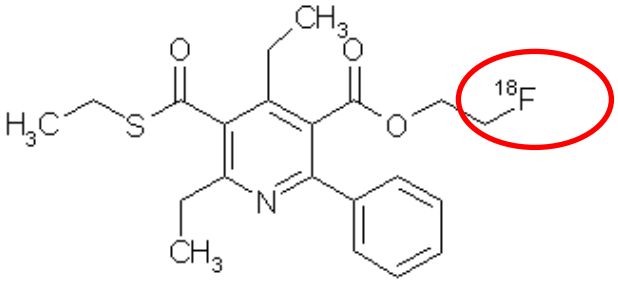
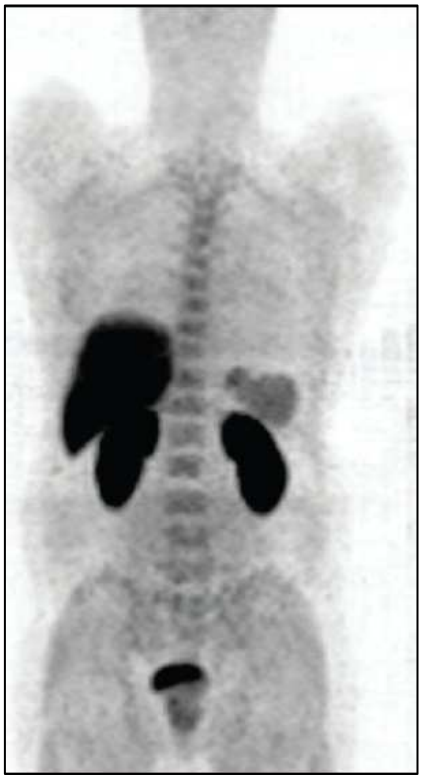
Why choline PET/CT ?



- Essential component of phospholipids and cell membrane metabolism
- Choline is incorporated into cell membrane phospholipids through phosphorylcholine synthesis *RoivainenA et al 2000*
- Choline is phosphorylated by choline kinase & trapped in the cell
- Malignant tumours increased cell membrane metabolism, increased choline use and increased CK expression (enzyme which phosphorylates choline)

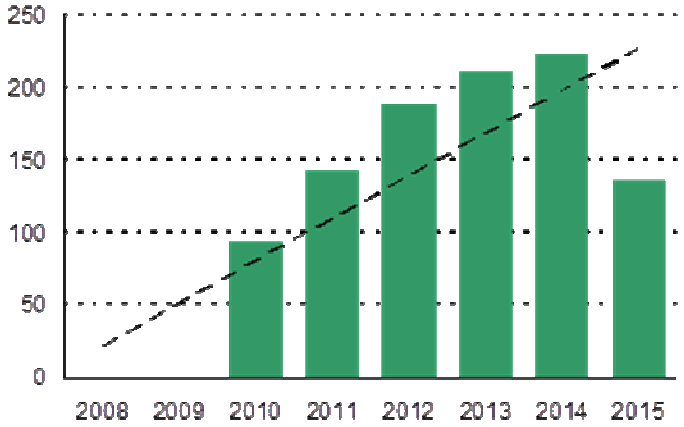
Ackerstaffet al, Can Res 2001

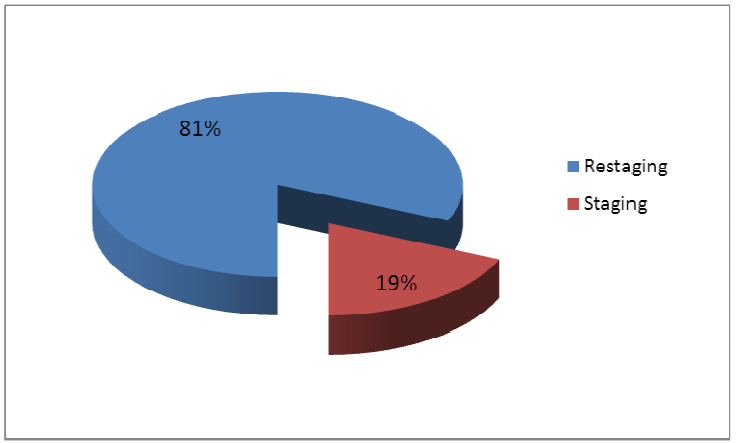


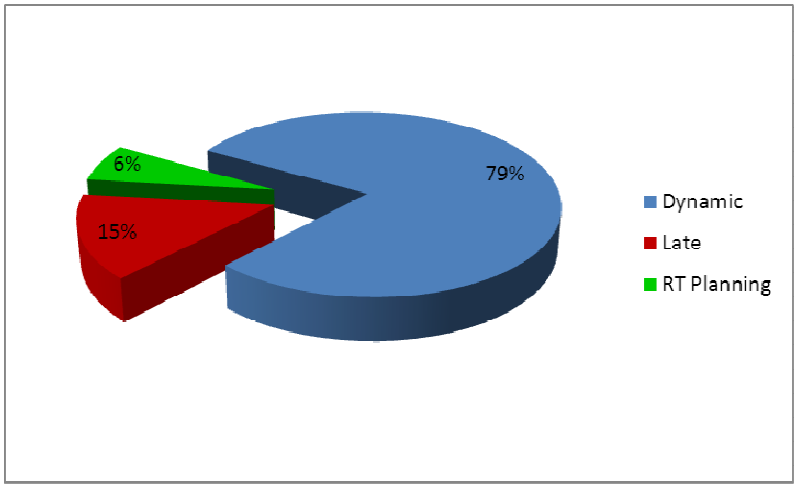
Indications

- ~~Diagnosis~~
- ~~Localization~~
- Primary staging
- Biochemical relapse post radical therapy (rising PSA, PSA derivates eg, PSA velocity and PSA doubling time are equally related to the likelihood of positive PET scan)
- Radiation therapy planning
- Response assessment
- Salvage and systemic therapy

18F-FCH PET/CT AT AOU-PR

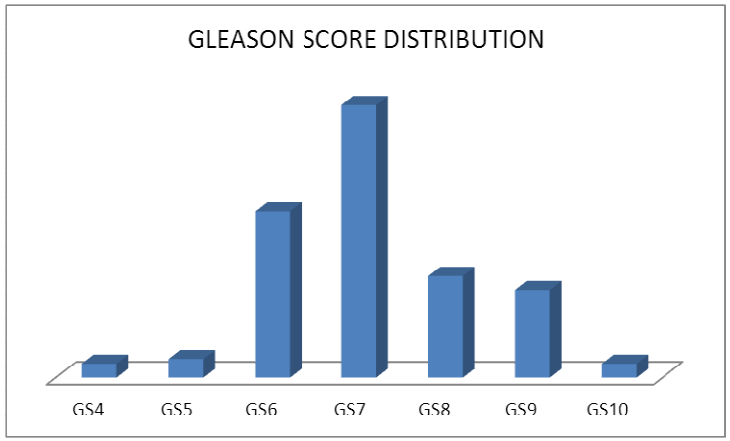


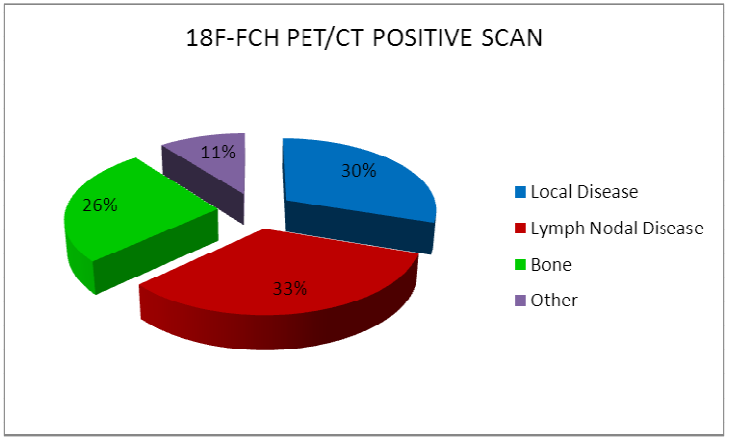


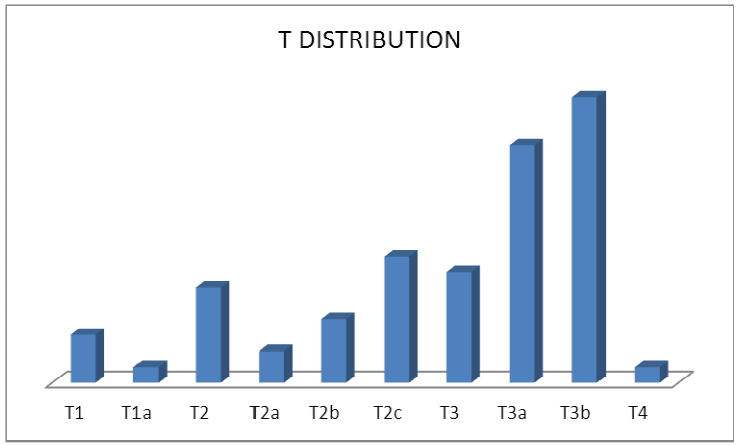


TREATMENTS BEFORE PET/CT	PTS%
RADICAL PROSTATECTOMY	58
RADIATION THERAPY	24
ANDROGEN DEPRIVATION THERAPY	43
COMBINED THERAPHY	43

18F-FCH PET/CT AT AOU-PR – PATIENTS CHARACTERISTICS

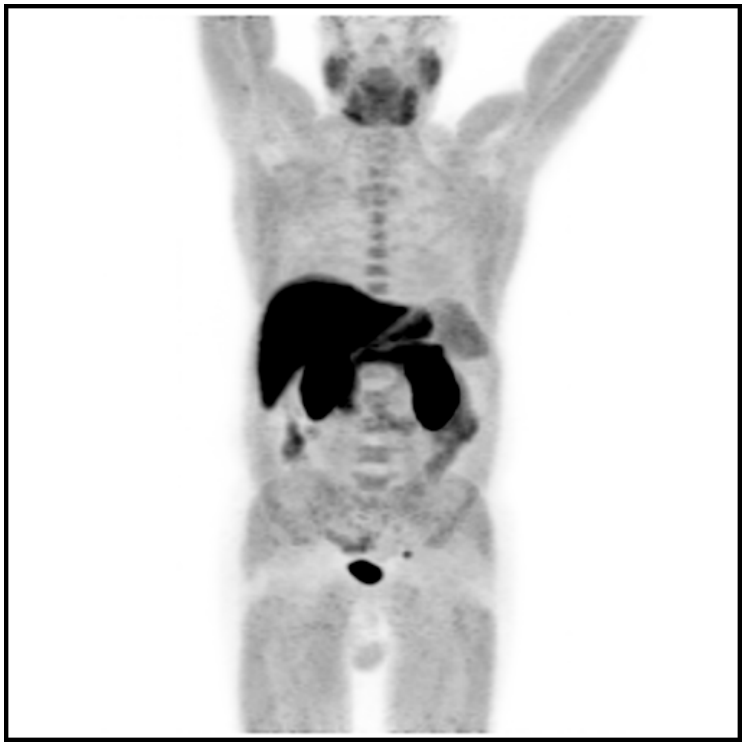


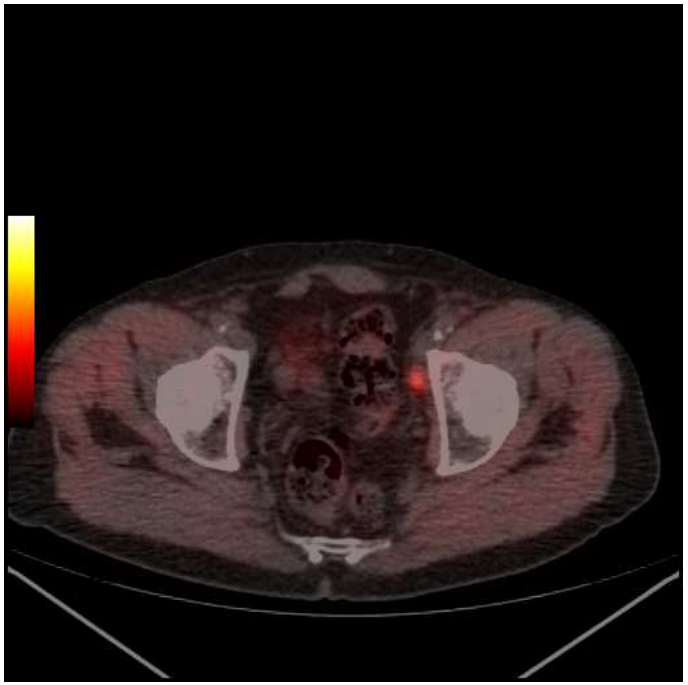




994 pts	
AGE AVERAGE	72 ± 15yrs
AGE RANGE	47-88yrs

Restaging prostate cancer: biochemical relapse

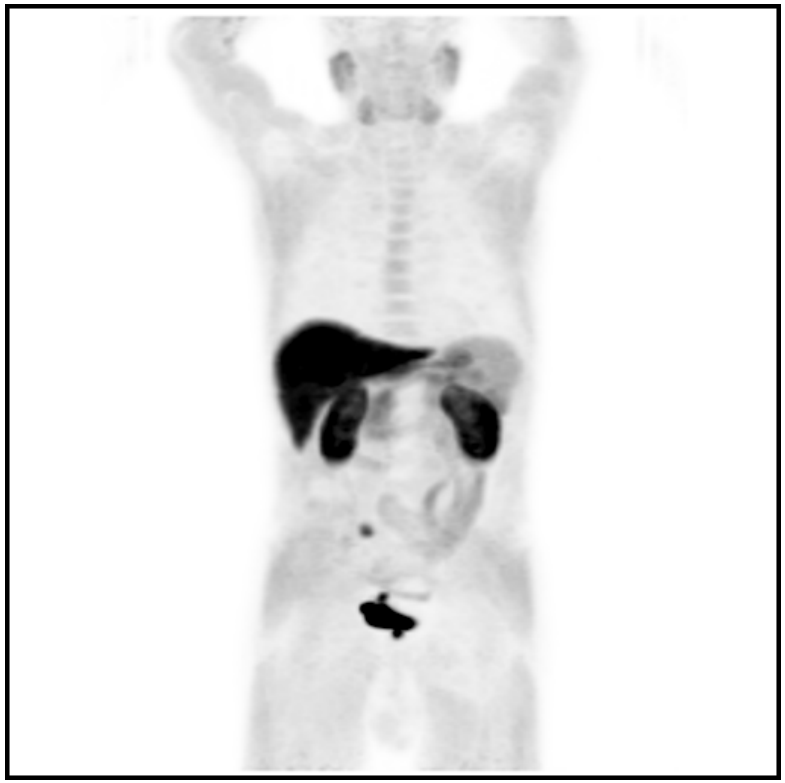


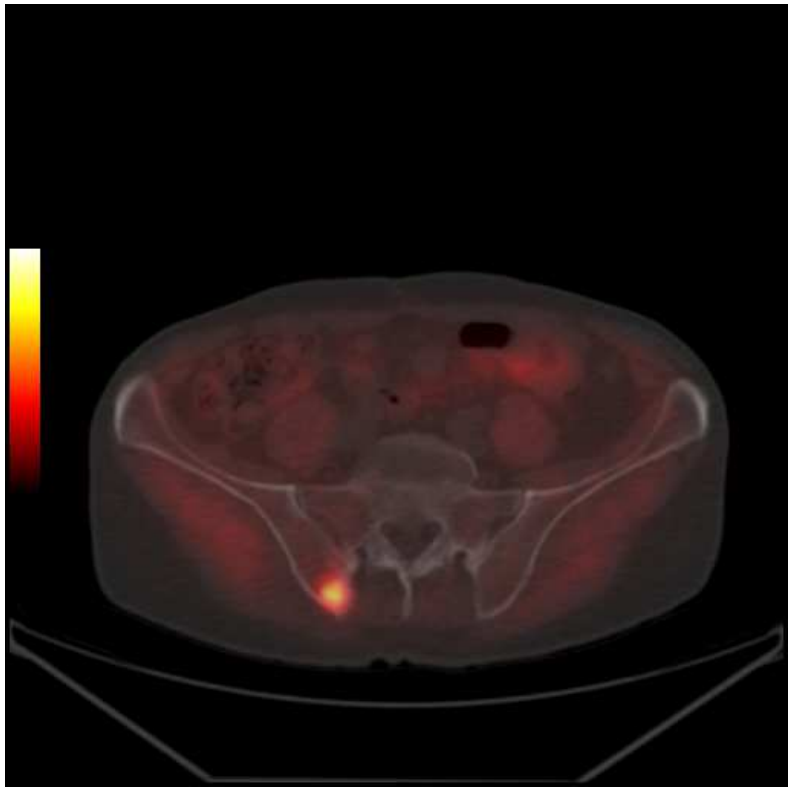


78 yrs
2007 radical prostatectomy ADC GS 7.
2010 increased level of PSA : Oct **2.1** ng/ml; Nov **2.48** ng/ml.
05.11.10 PET: solitary left obturator nodal lesion

Tracer: 18F-choline

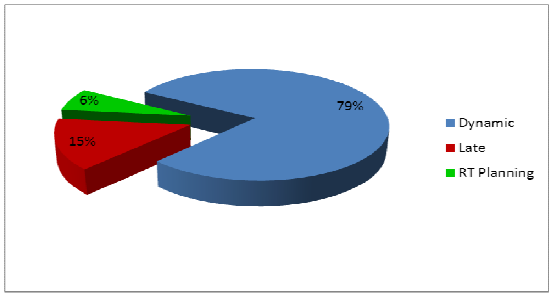
Restaging prostate cancer at low PSA values:
biochemical relapse

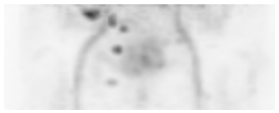




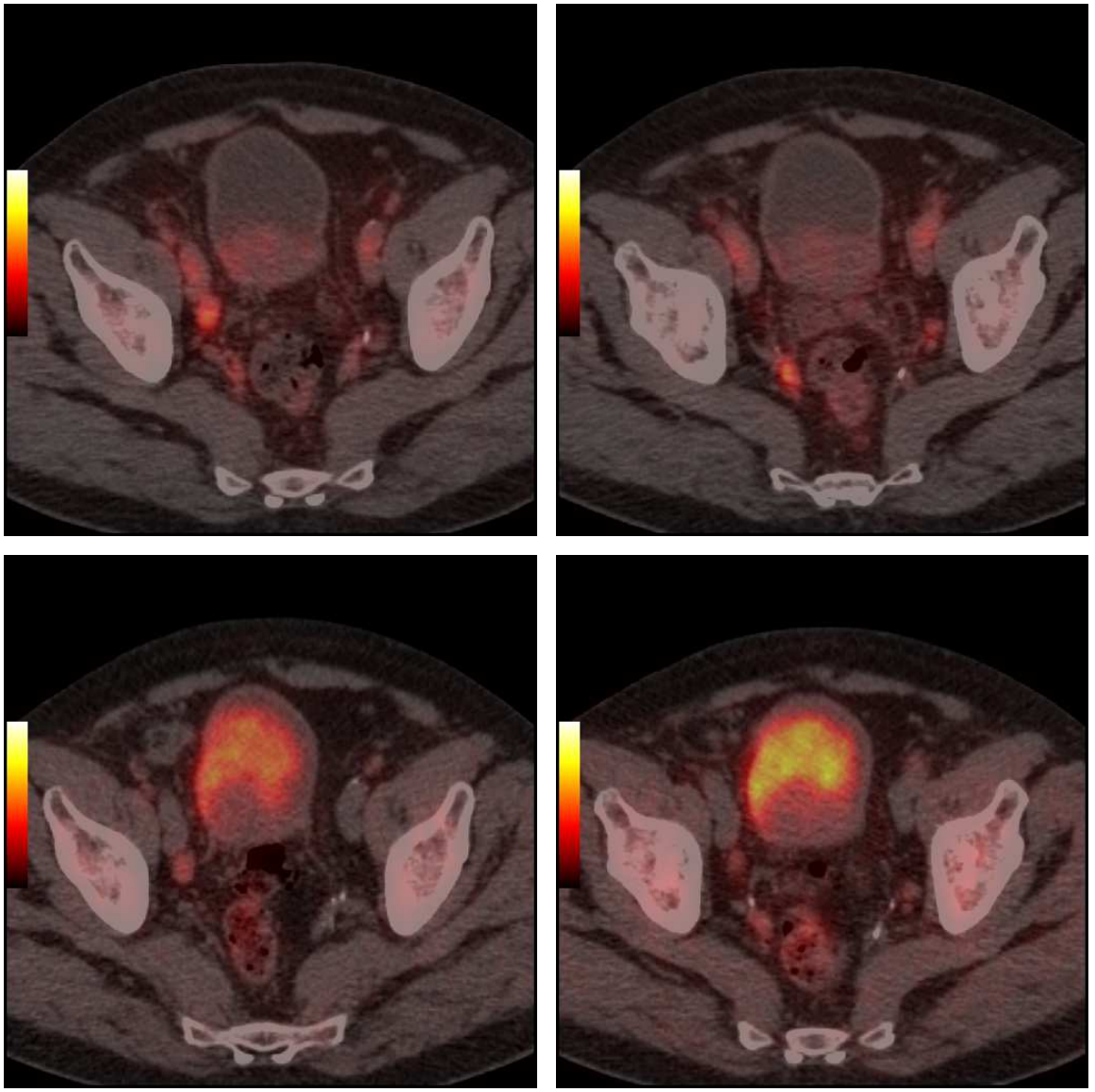
72 yrs
2001 partial prostatectomy ADC GS 8.
2008 increased level of PSA, → RT.
2011 increased level of PSA : 2011Aug **1.10** ng/ml;
2012 Feb **1.7** ng/ml.
23.03.12 PET: solitary bone lesion

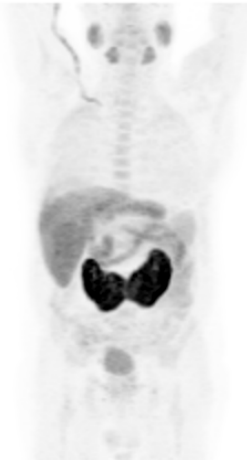
Tracer: 18F-choline





Early dynamic acquisition





Delayed whole body

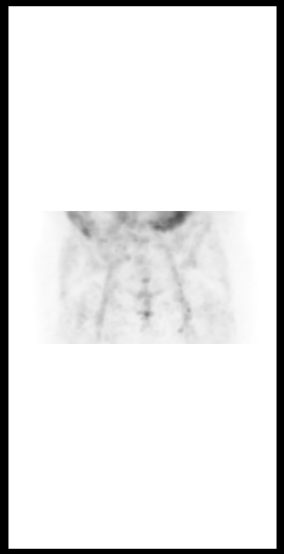
Flogistic lymph nodes with mild to moderate metabolic activity on PET showed a decreasing SUVmax on delayed images

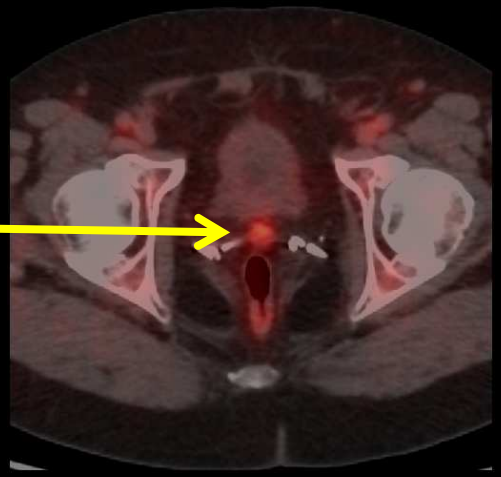
Restaging

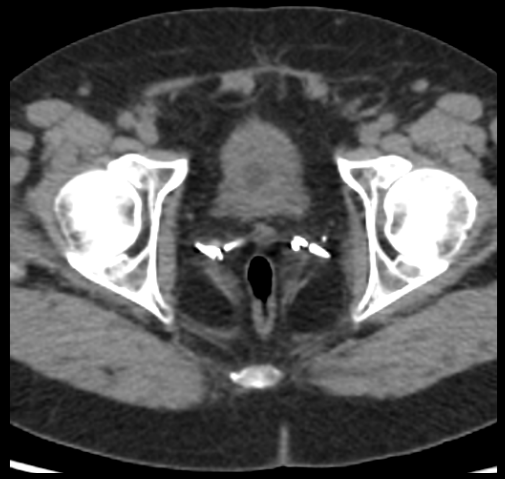
18F-FCH

2011 RP ADK G7 pT3a
12/2014 PSA 2.7 ng/ml
2/2015 PSA 4.6 ng/ml
3/2015 PSA 5.7 ng/ml
04/2015 FCH PET

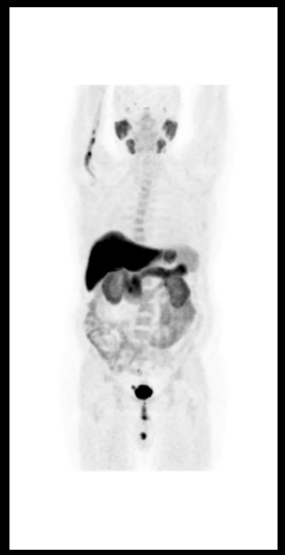
Early dynamic

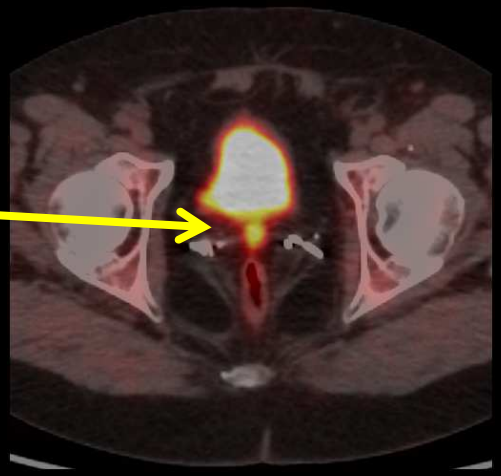


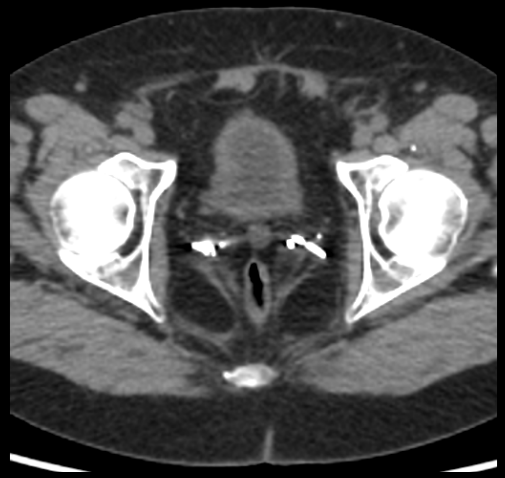




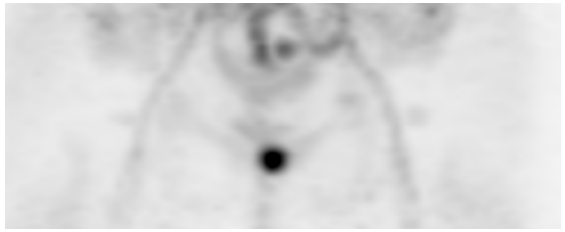
Late whole body

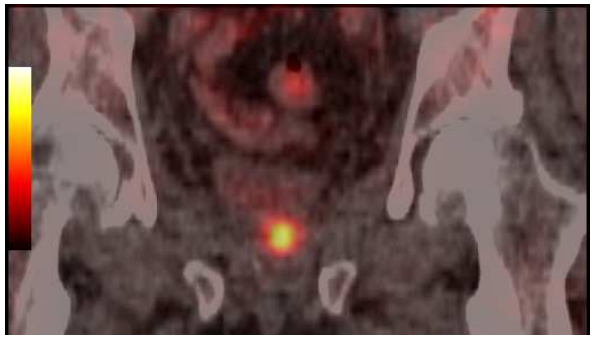


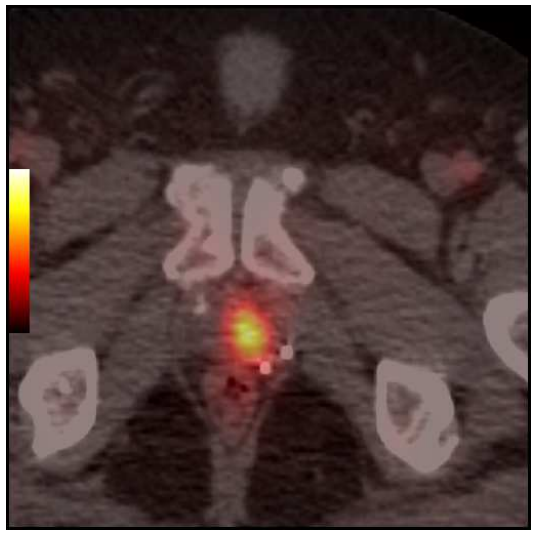


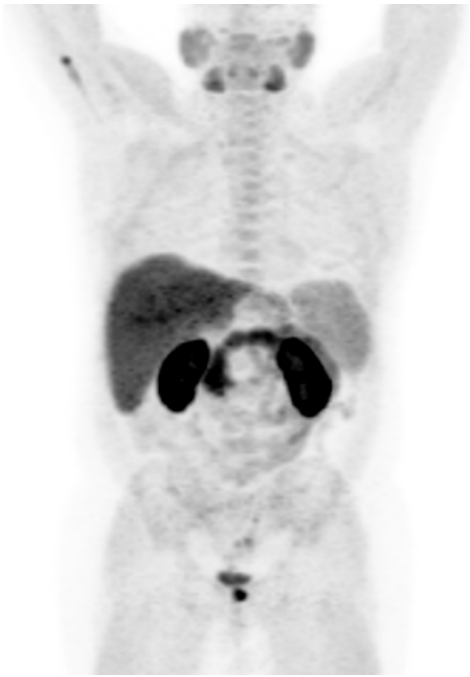


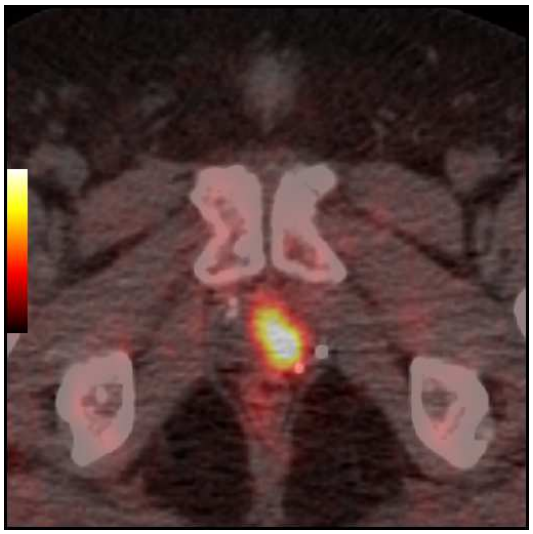
Delayed vs dynamic acquisition: differentiating local recurrences from urinary activity





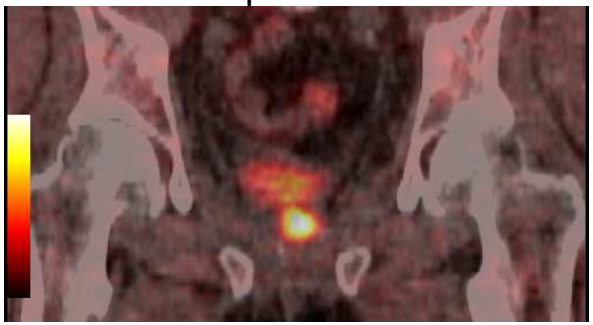


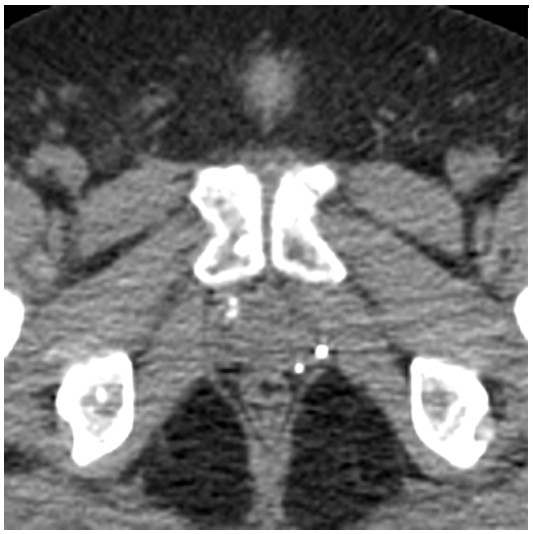




Restaging

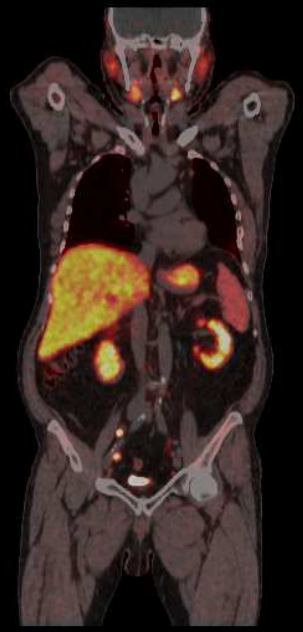
2010 PR ADK GS10 pT3b pN1
Ormonal therapy
PSA 01/2011 0.21 ng/ml
02/2011 0.45 ng/ml
05/2011 1.40 ng/ml
05.05.11 PET positive local recurrence

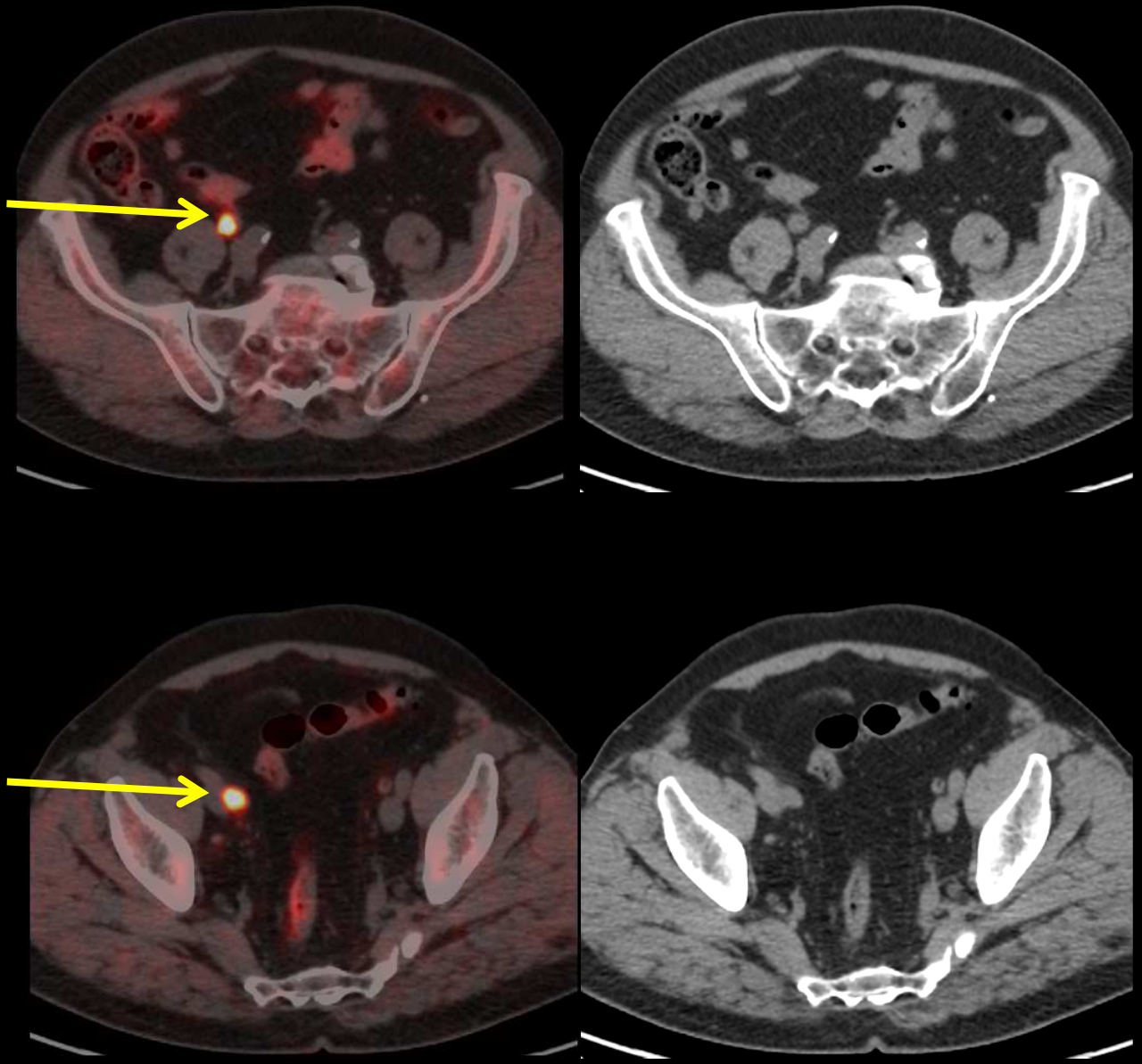




Restaging

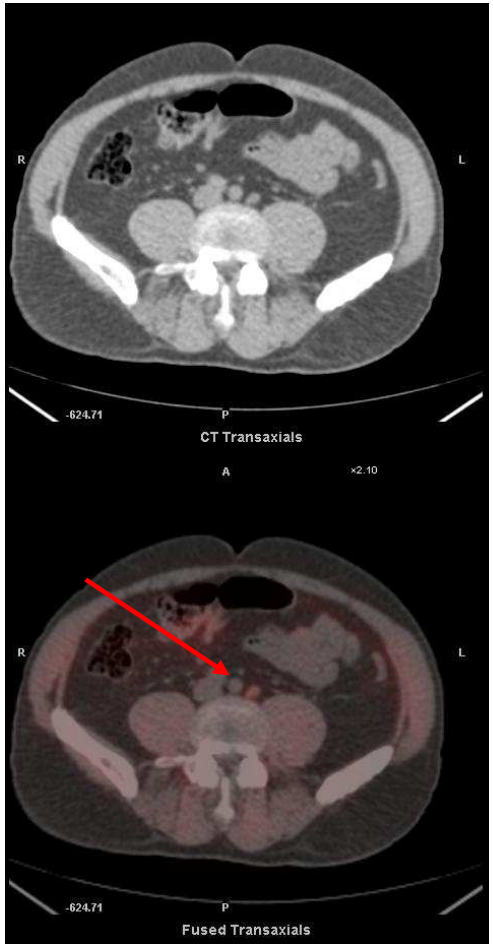
18F-FCH

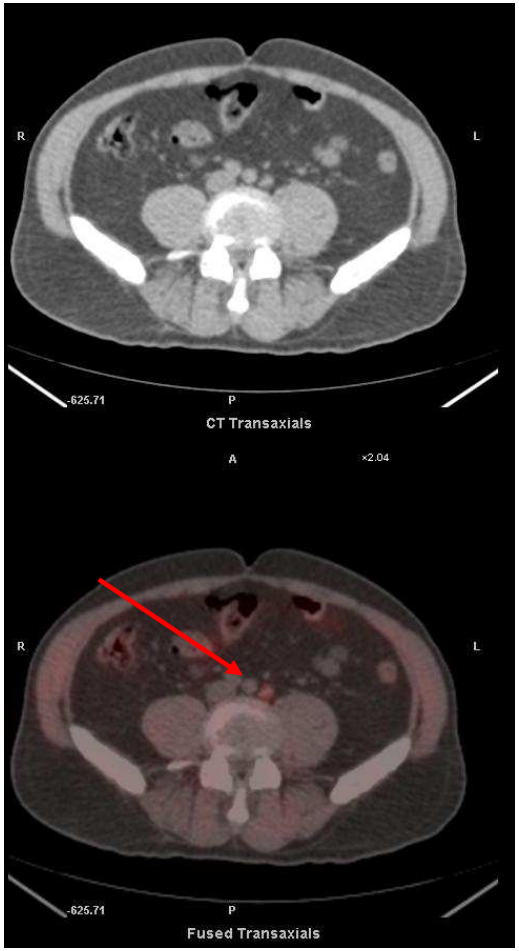


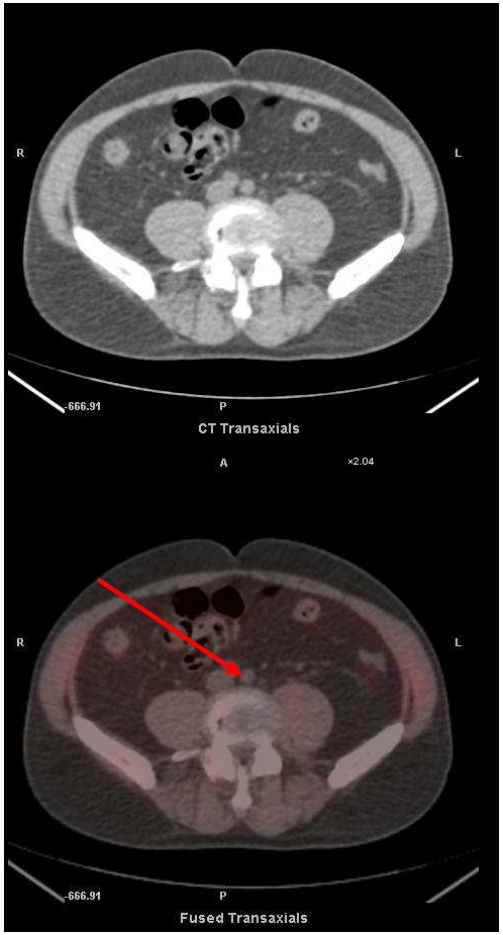


2012 ADK G7, RP
7/2014 PSA 1.51 ng/ml
12/2014 PSA 2.35 ng/ml
2/2015 PSA 3.9 ng/ml
02/2015 FCH PET

Monitoring treatment response after RT: CR



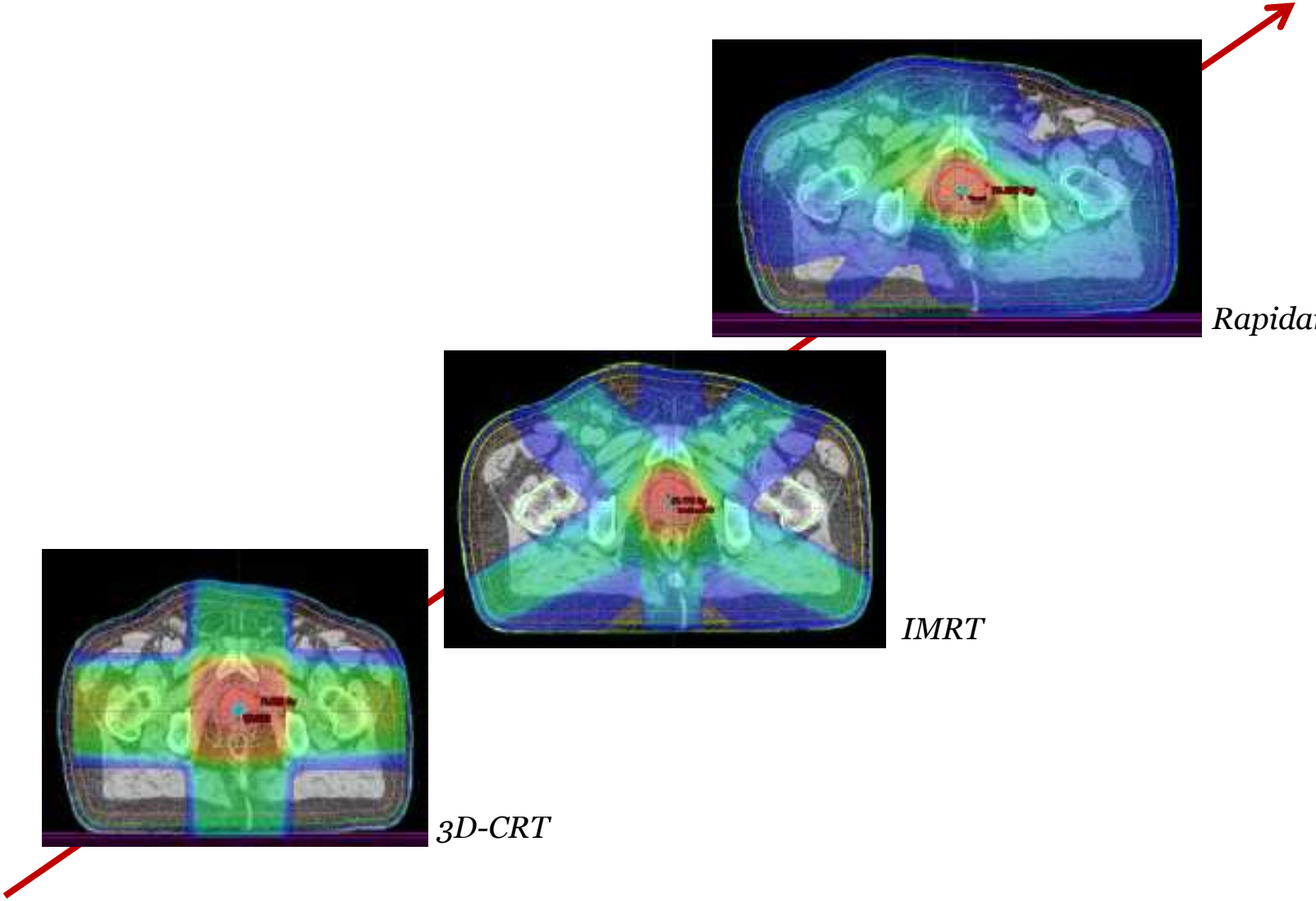




65 yrs
Apr 2010 PSA 3.51 ng/ml
Nov 2010 PSA 6.10 ng/ml
Nov 2010 solitary FCH uptake in left iliac LN
June 2011 repeated PET: solitary left iliac LN lesion → RT
June 2013 PSA 0.5 ng/ml, PET CR

Tracer: 18F-choline

RADIOTHERAPY

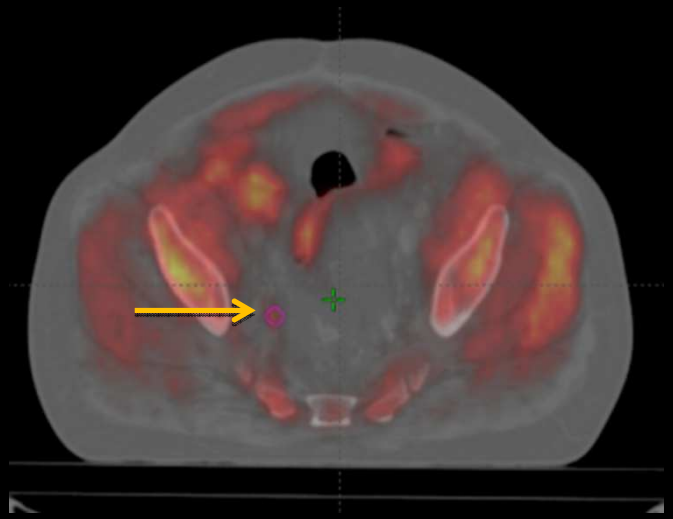


Rapidarc

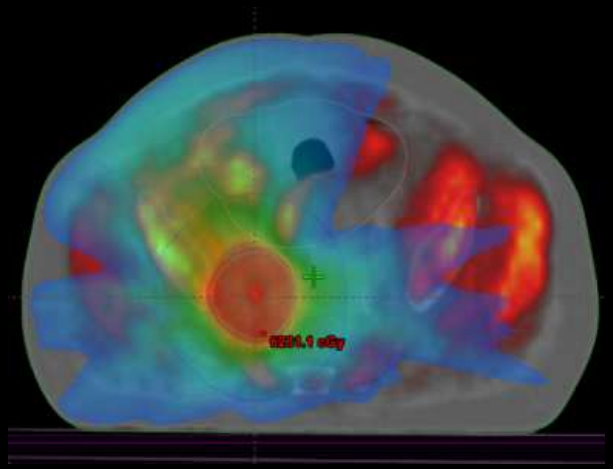
IMRT

3D-CRT

DOSE PAINTING FOR RADIATION TREATMENT PLANNING



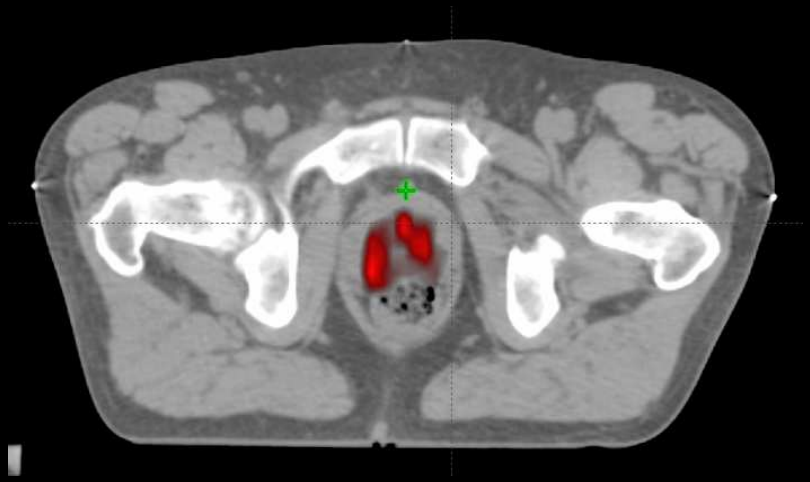
18F-FCH PET/CT LOCALIZES A SINGLE REGIONAL LYMPH NODE DISEASE



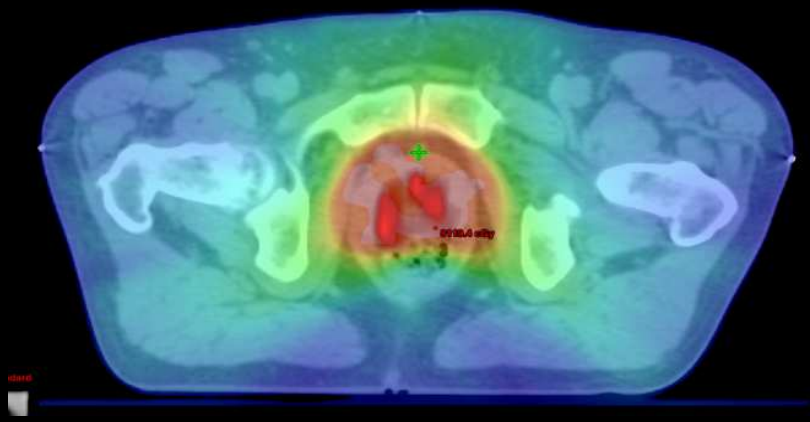
RT PLANNING

Previous prostatectomy

DOSE PAINTING FOR RADIATION TREATMENT PLANNING

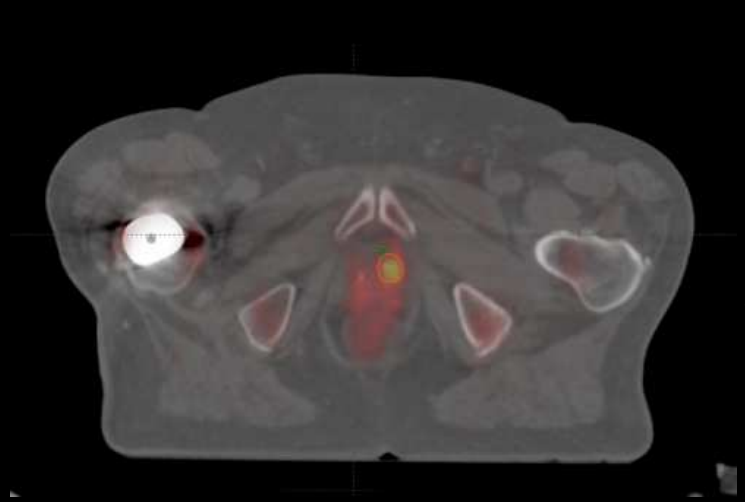


18F-FCH PET/CT SHOWS ONLY LOCAL DISEASE

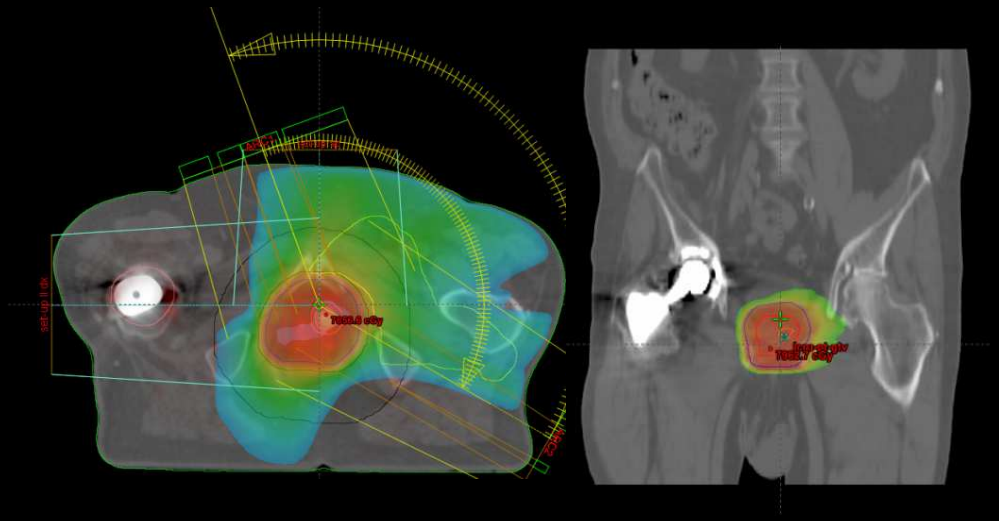


RT PLANNING: high dose on disease localization only (red)

DOSE PAINTING FOR RADIATION TREATMENT PLANNING



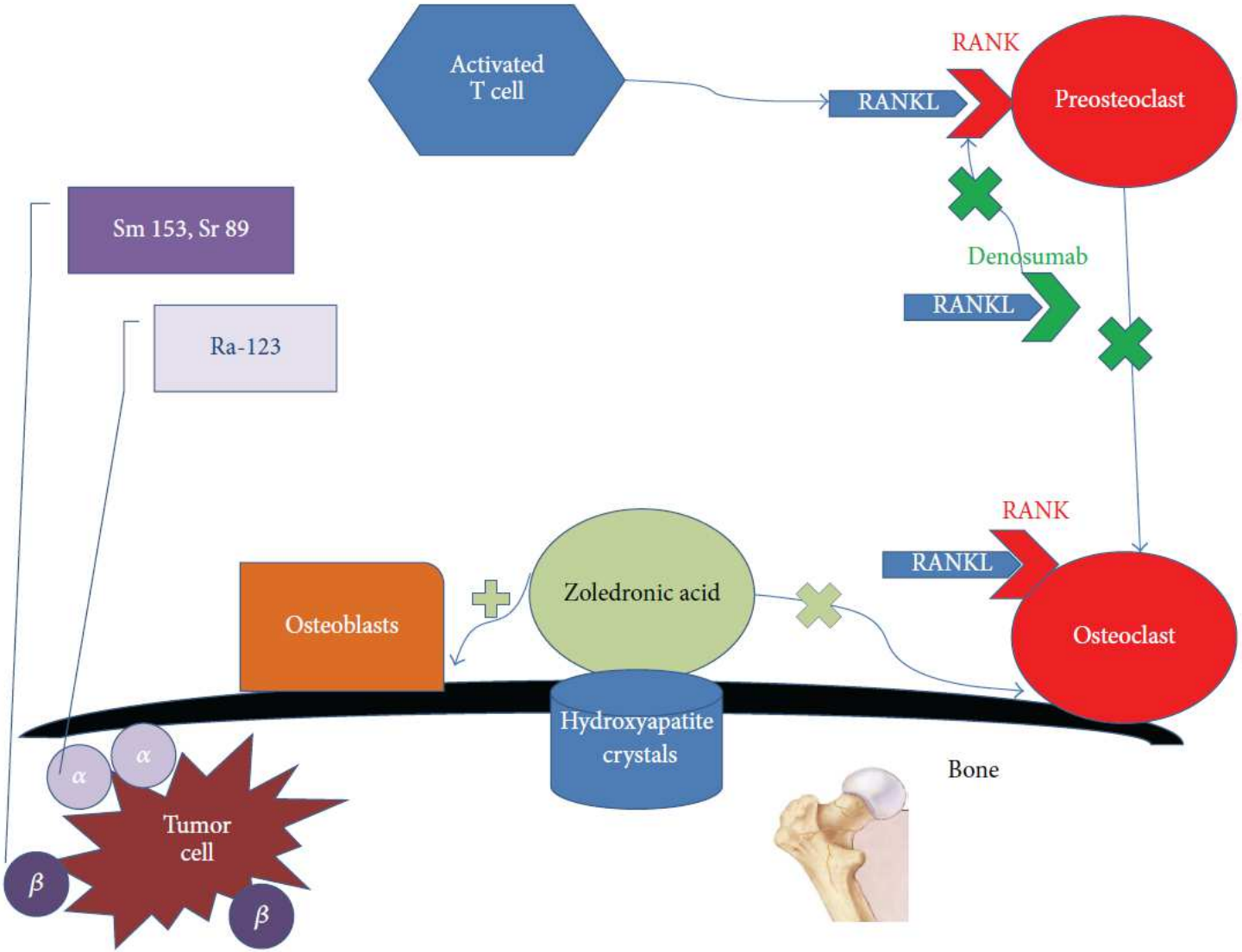
LOCAL DISEASE UPTAKE



RADIATION TREATMENT PLANNING
High dose on disease localization, avodied radiation dose to hip prosthesis

Prostate cancer eligible to radiation theraphy (Hip prosthesis)

Bone-targeted therapies in mCRPC



- Zoledronic acid binds to hydroxyapatite crystals preventing the activity of osteoclasts and stimulating osteoblast.
- Denosumab binds to RANKL preventing the binding of RANKL to RANK thus inhibiting activation of osteoclasts.
- Radiopharmaceuticals emit or ionizing radiation to the tumor cell in the bone

Bone-targeting radiopharmaceuticals

- Bone-targeting radiopharmaceuticals have been studied clinically as a treatment of cancer that has metastasized to the skeleton.
- Systemic therapy using bone-seeking radiopharmaceuticals has clear advantages for the treatment of **multisite** metastatic pain. Appropriate patient selection relies on correlating clinical symptoms with focal abnormalities on bone scintigraphy.
- Time to symptom relief and response duration vary with the physical half-life and dose rate of the **radionuclide used**, offering the opportunity to tailor radiopharmaceutical choice to individual patient circumstances.
- Toxicity is limited to **temporary myelosuppression**, governed by the administered activity and underlying bone marrow reserve.
- Optimal responses are achieved in patients with a modest skeletal tumor burden, suggesting that targeted therapy should be considered **early** in the management of bone metastases.

Main physical properties of different radionuclides in clinical used or under research for palliative treatment of bone metastases.

Radionuclide	Emission type	E (MeV) (%)	E γ (KeV) (%)	T 1/2 (days)	Tissue penetration range (mm)
^{32}P	β^-	0.6955 (100)	–	14.3	8.0
^{89}Sr	β^-	0.5846 (99.99)	909 (0.1)	50.5	6.7
^{90}Y	β^-	0.2670 (99.98)	–	2.67	2.7
^{117m}Sn	Auger	0.1268 (64.8)	159 (86)	13.6	0.3
^{153}Sm	β^-	0.2253 (48.2)	103 (28)	1.93	3.4
^{166}Ho	β^-	0.6511 (50.5)	81 (6.4)	1.12	8.6
^{170}Tm	β^-	0.3231 (81.6)	84 (3.3)	127.8	5
^{177}Lu	β^-	0.1494 (79.3)	211 (11)	6.2	1.8
^{186}Re	β^-	0.3596 (70.9)	137 (9)	3.8	4.7
^{188}Re	β^-	2.1204 (71.1)	155 (15)	0.7	2.4
^{223}Ra	α	5.71581 (45.6)	154 (5.6)	11.4	0.1

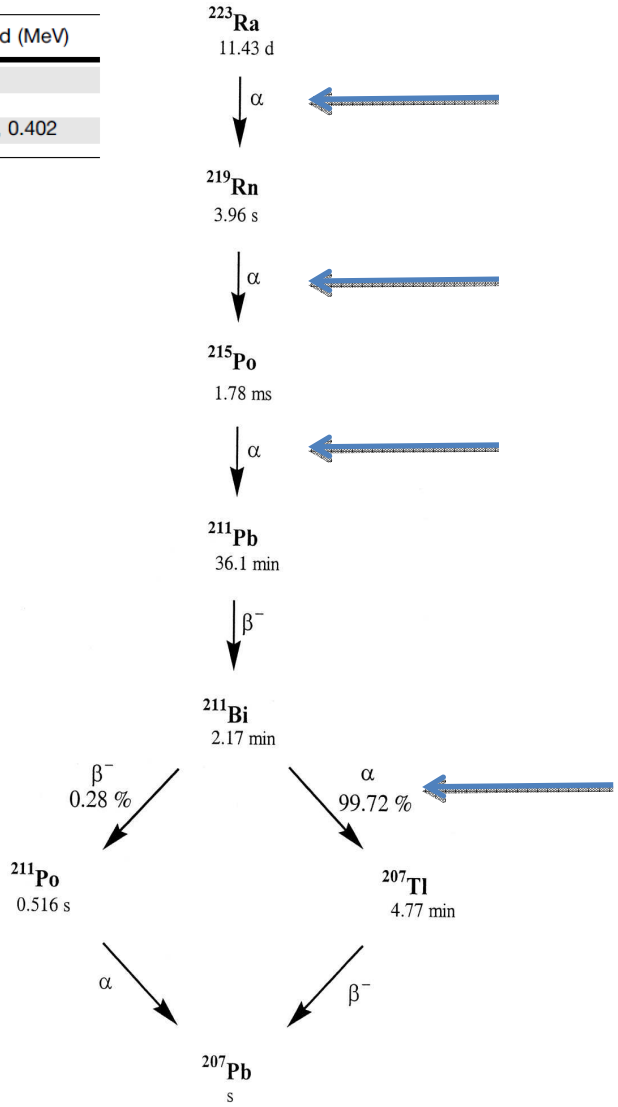
Radium-223 favorable features in radionuclide therapy

- It can be produced relatively inexpensively, readily, and in large amounts: sources of ^{227}Ac ($t_{1/2}$ = 21.7 years) could potentially be used as a long-term operating generator for ^{223}Ra.^{227}Ac can in turn be produced by neutron irradiation of relatively commonly available ^{226}Ra
- ^{223}Ra has a physical **half-life of 11.4 days**, which provides sufficient time for preparation, distribution, including long distance shipment, and administration of the α-emitting radionuclide
- Because of the bone-seeking properties of **alkaline earth elements** (Ca, Sr, Ba, and Ra), Ra^{2+} may be useful for metabolically concentrated radionuclide irradiation of osseous sites *e.g.*, bone surfaces and skeletal metastases growth zones.
- This allows a **deeper incorporation into the bone matrix** before decay occurs, and less radiation to soft tissues during the uptake and elimination phase because a lower fraction of the injected radium atoms would decay in the first few days

Decay of ^{223}Ra

Half-life (d)	Path length (μm), mean/maximum	Emission	Maximum energy deposited (MeV)
11.43	60–100	α (4)	5.78, 6.88, 7.53, 6.68
		β (2)	0.45, 0.49
		γ (5)	0.82, 0.154, 0.269, 0.351, 0.402

- ^{223}Ra decays through a multistep chain chain releasing α-, β- and γ-particles with the emission of approximately 28 MeV of energy.
- The fraction of energy borne by particulate radiation emitted as α-particles is ~96%
- ^{223}Ra is excreted by the small intestine.



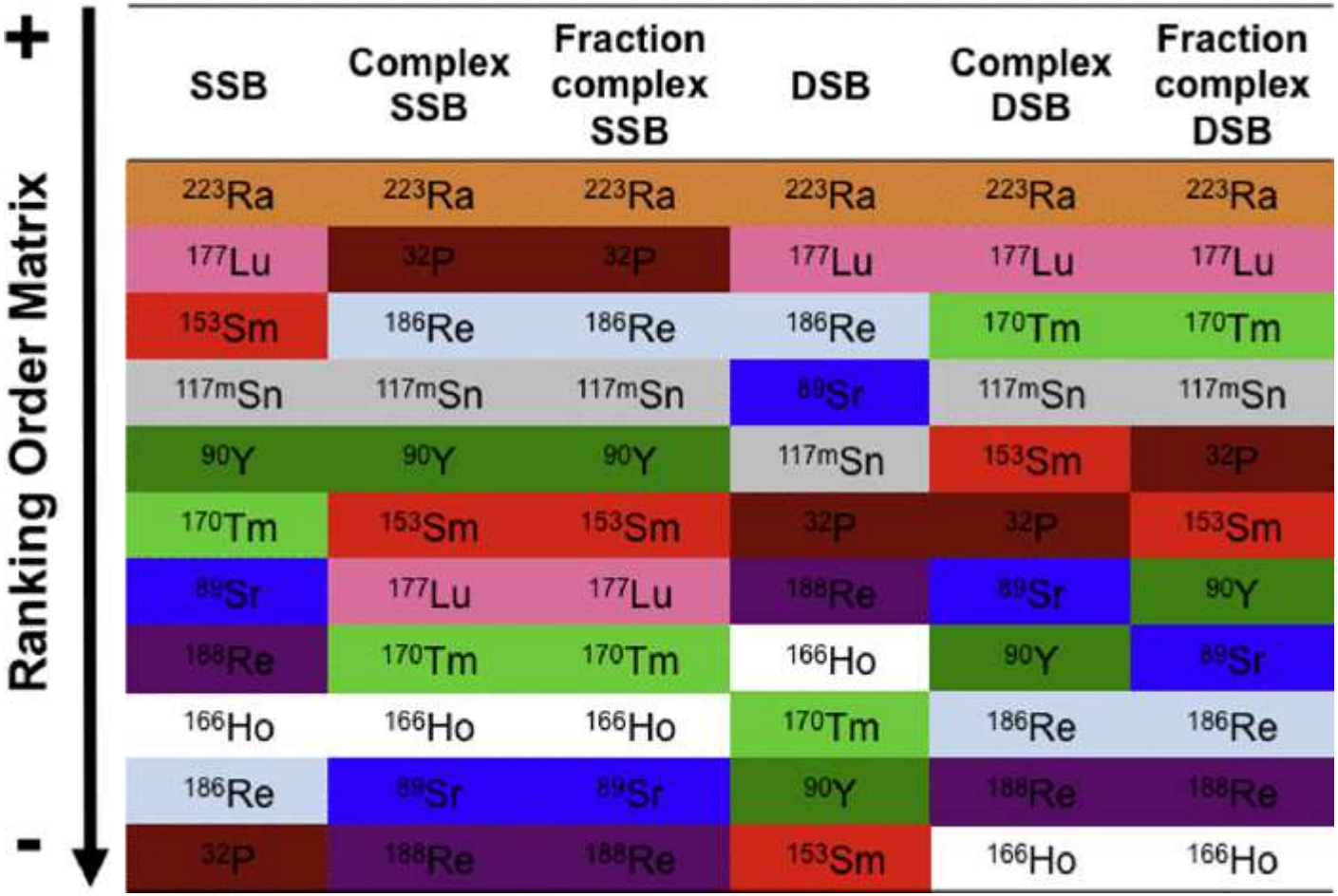
Dosimetry and indications

Organ	cGy/37 MBq
Bone surface	4,262.60
Red bone marrow	513.51
Lower bowel wall	171.88
Urinary bladder wall	14.9
Testes	0.31
Ovaries	1.8
Uterine wall	0.94
Kidney	11.86

Category	Description
Indications	Skeletal metastasis in castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral metastatic disease
Contraindications	Pregnancy, breast-feeding, and women of child-bearing age
Prerequisites	
First dose	ANC $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and hemoglobin ≥ 10 g/dL
Subsequent doses	ANC $\geq 1 \times 10^9$/L and platelet count $\geq 50 \times 10^9$/L (discontinue if hematologic values do not recover within 6–8 wk after last administration despite supportive care)

ANC = absolute neutrophil count

Radiation-induced DNA damages obtained post-irradiation with different radioactive particles emitted by selected radioisotopes for palliative treatment of bone metastases



DNA damages categorization
- no damage
- single-strand breaks (SSBs)
- two strand breaks on the same strand (SSB^+)
- two or more strand breaks on opposite strands separated by at least ten base pairs (2SSB)
- two strand breaks on opposite strands with a separation not greater than ten base pairs [double-strand breaks (DSBs)]

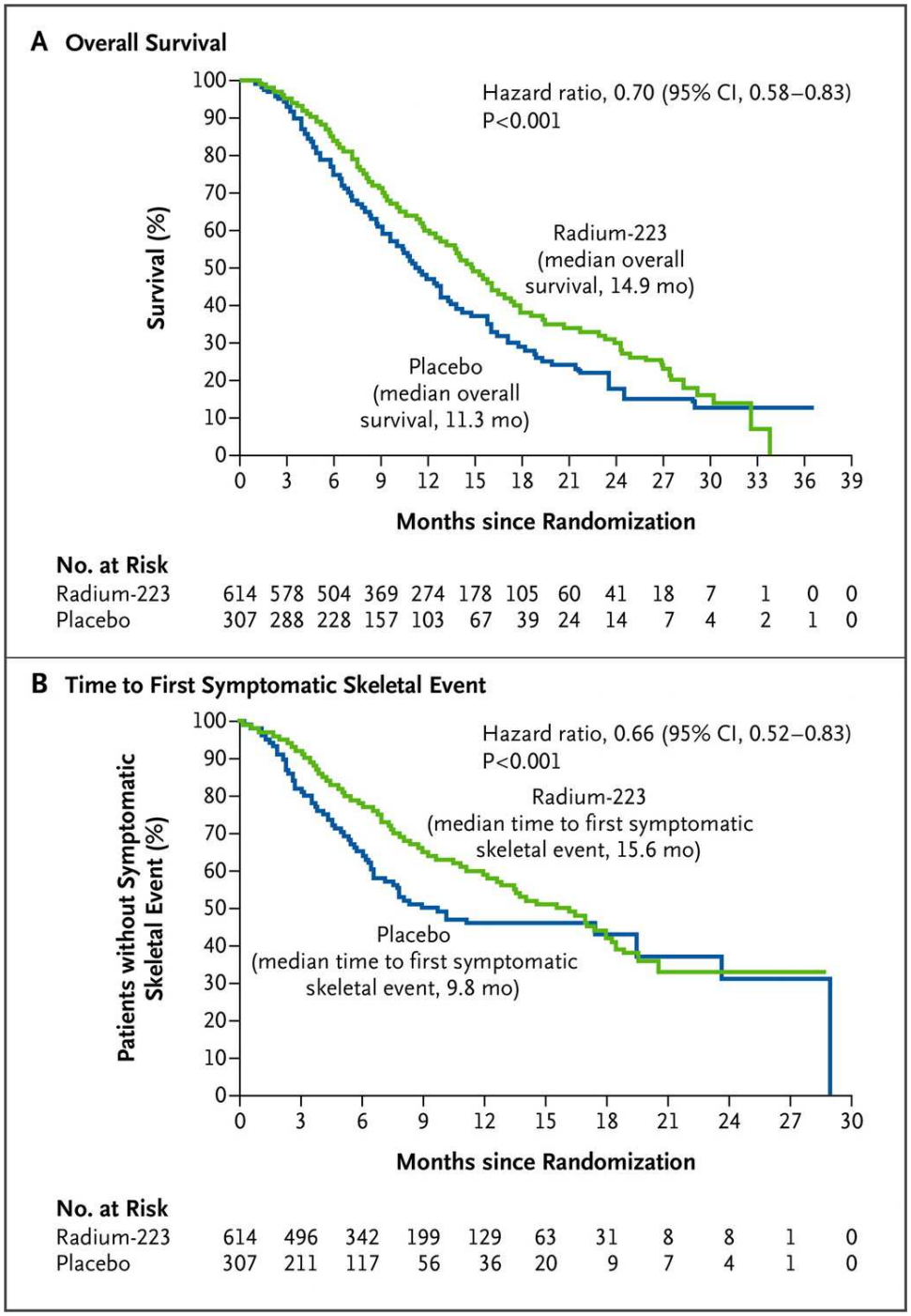
Medical Physics, Vol. 41, No. 11, November 2014

Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial

Peter Hoskin, Oliver Sartor, Joe M O'Sullivan, Dag Clement Johannessen, Svein I Helle, John Logue, David Bottomley, Sten Nilsson, Nicholas J Vogelzang, Fang Fang, Mona Wahba, Anne-Kirsti Aksnes, Christopher Parker

- Current bone-targeted therapies for patients with CRPC are palliative, and the benefit of bisphosphonates and denosumab is limited to delaying SREs with no improvement in survival or quality of life.
- The ALSYMPCA trial was designed to compare the efficacy, in terms of overall survival (OS), and safety of radium-223 plus best standard of care (BSC) versus placebo plus BSC in patients with bone metastases from CRPC.

Lancet Oncol 2014



Kaplan–Meier Estimates of Overall Survival and the Time to the First Symptomatic Skeletal Event

Lancet Oncol 2014