Optimising patient care in metastatic prostate cancer

Inaugural Malaysian Nuclear Medicine Conference

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Prostate cancer

- Most common non-cutaneous cancer in men in UK
- Second most common cancer overall
- Approximately 46,700 new cases of prostate cancer diagnosed in UK in 2014
- 13% of all new cancer cases in men and women
- Around 11,200 men died from prostate cancer in the UK in 2014

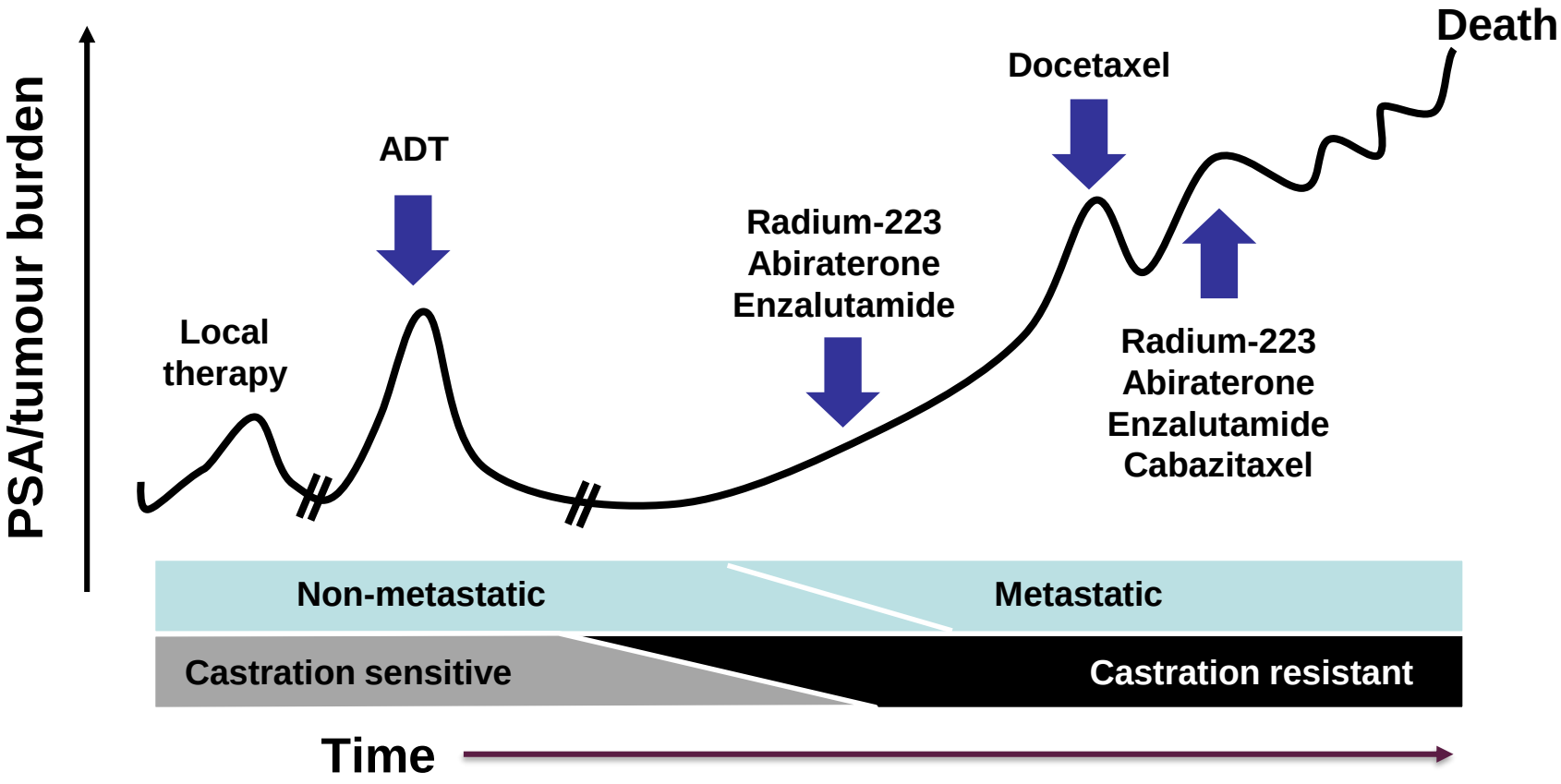
Prostate cancer

- Most patients diagnosed with early-stage disease
- 17–34% have metastases at diagnosis
- Metastases most frequently in the bones, occurring in up to 90% of patients
- 30% with castration-resistant disease develop visceral metastases
- From presentation of metastatic disease, median overall survival (OS) is reported as 42.1 months
- While currently available treatments may improve survival, there is still no cure for metastatic castration resistant prostate cancer (mCRPC)

Bone metastases in prostate cancer

- Bone metastases result in :
  - pain
  - skeletal related events (SRE)
  - disability & death
  - reduced quality of life
  - reduced overall survival
  - increased health burden & treatment costs
- Disease and treatment related symptoms affect QOL
- Non-skeletal symptoms include fatigue, GI effects, GU dysfunction, anxiety, sleep disturbances,rash

Prostate cancer disease continuum: mCRPC treatment options 2018



George D. Urology 2013. Available at: ttp://www.webedcafe.com/extern/program_media/goldjournal.net/2013/prostate_cancer/figure.php?speaker=george&figure=3. Accessed October 2015.

Treatments options in mCRPC

	Systemic agents	Radioisotopes
Agents that increase overall survival (OS)	Abiraterone Enzalutamide Docetaxel Cabazitaxel Sipuluecel-T	^{223} Radium
Palliative agents	Zoledronic acid Denosumab	^{89}SrCl2 ^{153}Sm EDTMP ^{186}Re HEDP ^{188}Re HEDP EBRT
Experimental agents	Darolutamide ProstVac (PSA targeted immunotherapy) Ipilimumab Galeterone (anti-androgen)	^{177}Lu PSMA ^{225}AcPSMA

Overall survival benefit in mCRPC

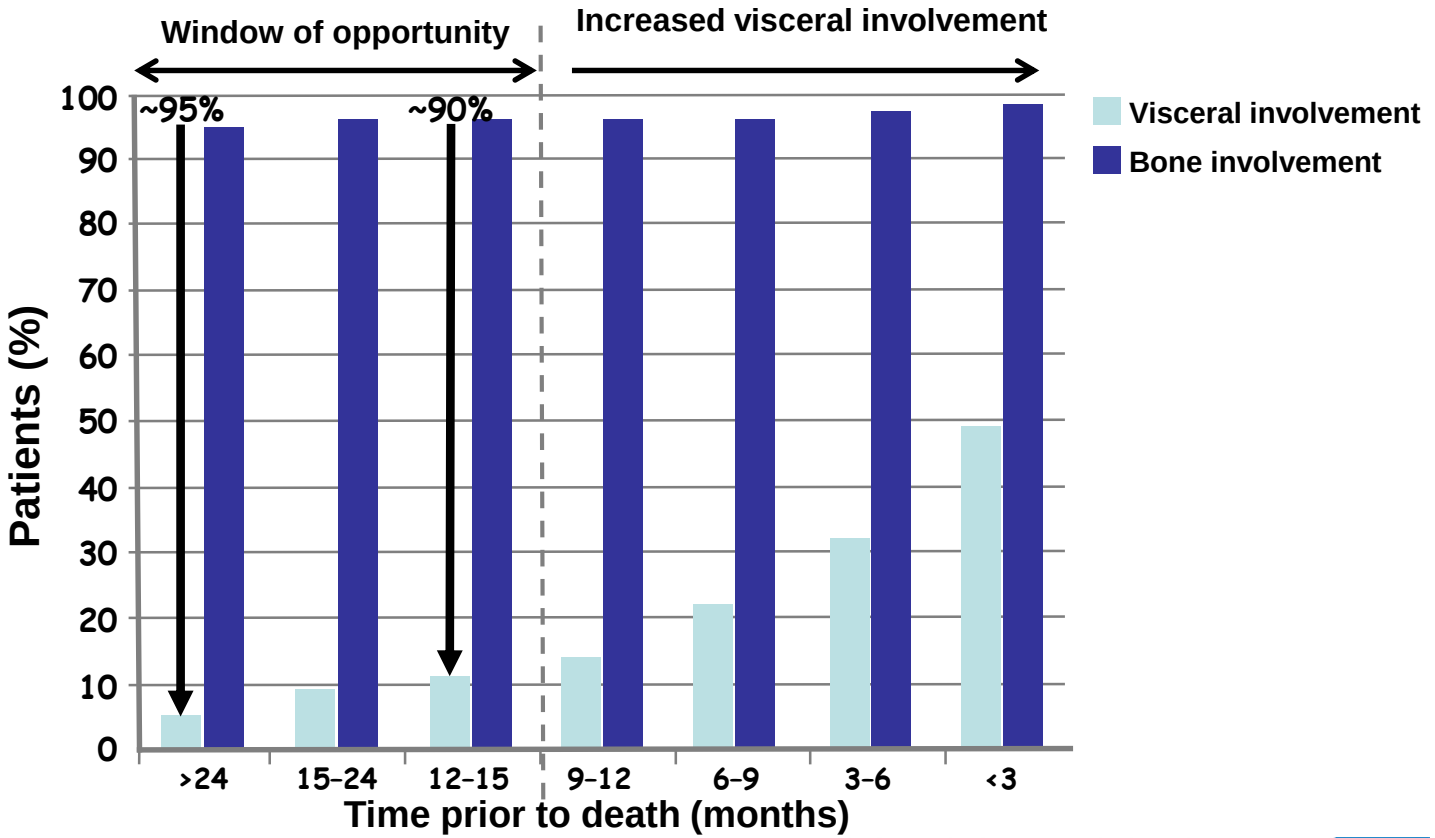
	Patient setting	Control	Overall survival		
			Increase in median, months	HR	*p* value
Docetaxel/P[1]	First-line	Mitoxantrone/P	2.9	0.79	0.004
Radium-223[2]	Bone metastases	Placebo	3.6	0.70	<0.001
Sipuleucel-T*[3]	Chemo-naïve	Placebo	4.1	0.78	0.03
Abiraterone/P[4]	Post-docetaxel	Placebo/P	4.6	0.74	<0.0001
Abiraterone/P[5]	Chemo-naïve	Placebo/P	4.4	0.81	0.0033
Enzalutamide[6]	Post-docetaxel	Placebo	4.8	0.63	<0.001
Enzalutamide[7]	Chemo-naïve	Placebo	2.2	0.71	<0.001
Cabazitaxel/P[8]	Post-docetaxel	Mitoxantrone/P	2.4	0.70	<0.0001

HR, hazard ratio; P, prednisone
*Sipuleucel-T was withdrawn from use in the European Union in May 2015

1. Berthold DR et al. J Clin Oncol 2008;26:242–5; 2. Parker C et al. N Engl J Med 2013;369:213–23;
3. Kantoff PW et al. N Engl J Med 2010;363:411–22; 4. Fizazzi K et al. Lancet Oncol 2012;13:983–92;
5. Ryan CJ et al. Lancet Oncol 2015;16:152–60; 6. Scher HI et al. N Engl J Med 2012;367:1187–97;
7. Beer T. N Engl J Med 2014;371:424–33; 8. de Bono JS et al. Lancet 2010;76:1147–54

Most patients with mCRPC are candidates for radium-223 treatment

Radium-223 is indicated for mCRPC with symptomatic bone metastases and no known visceral metastases, which mostly occur in the final disease stages



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Radium 223 Summary of Product Characteristics (SmPC), Bayer Pharma AG, 13342 Berlin, Germany, 2015;
Pezaro C et al. Eur Urol 2014;65:270−273

Treatment with radium-223

- Recommended for mCRPC patients with symptomatic bone metastases, with no visceral metastases
- Sensible to consider radium early in the course of mCRPC
- Clinical window of opportunity before visceral mets develop, this renders patient ineligible for radium
- Generally recommend less toxic treatments first
- Minimise treatment related effects on patient lifestyle and QOL
- Optimum sequence of life-prolonging therapies is unknown.

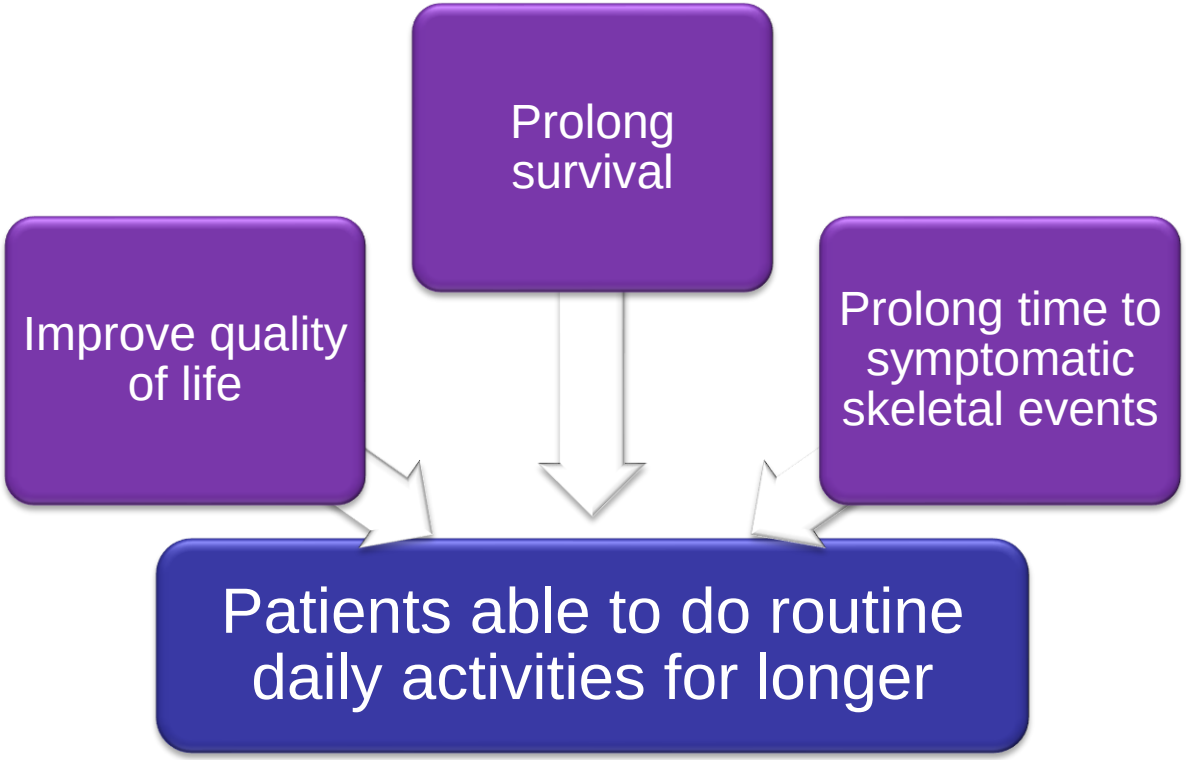
Radium-223 in symptomatic patients

- Recommended for mCRPC patients with symptomatic bone metastases, with no visceral metastases
- Similar OS improvement in minimally symptomatic and more symptomatic patients with mCRPC
- No need to delay treatment until symptoms are severe
- Main aim is to improve survival, not to relieve symptoms
- Before or after docetaxel chemotherapy?
- Consider chemotherapy if poor prognostic markers:
  - PSA doubling time < 6 months
  - Response to ADT <12 months
  - Extensive lymph node disease

Concomitant treatments

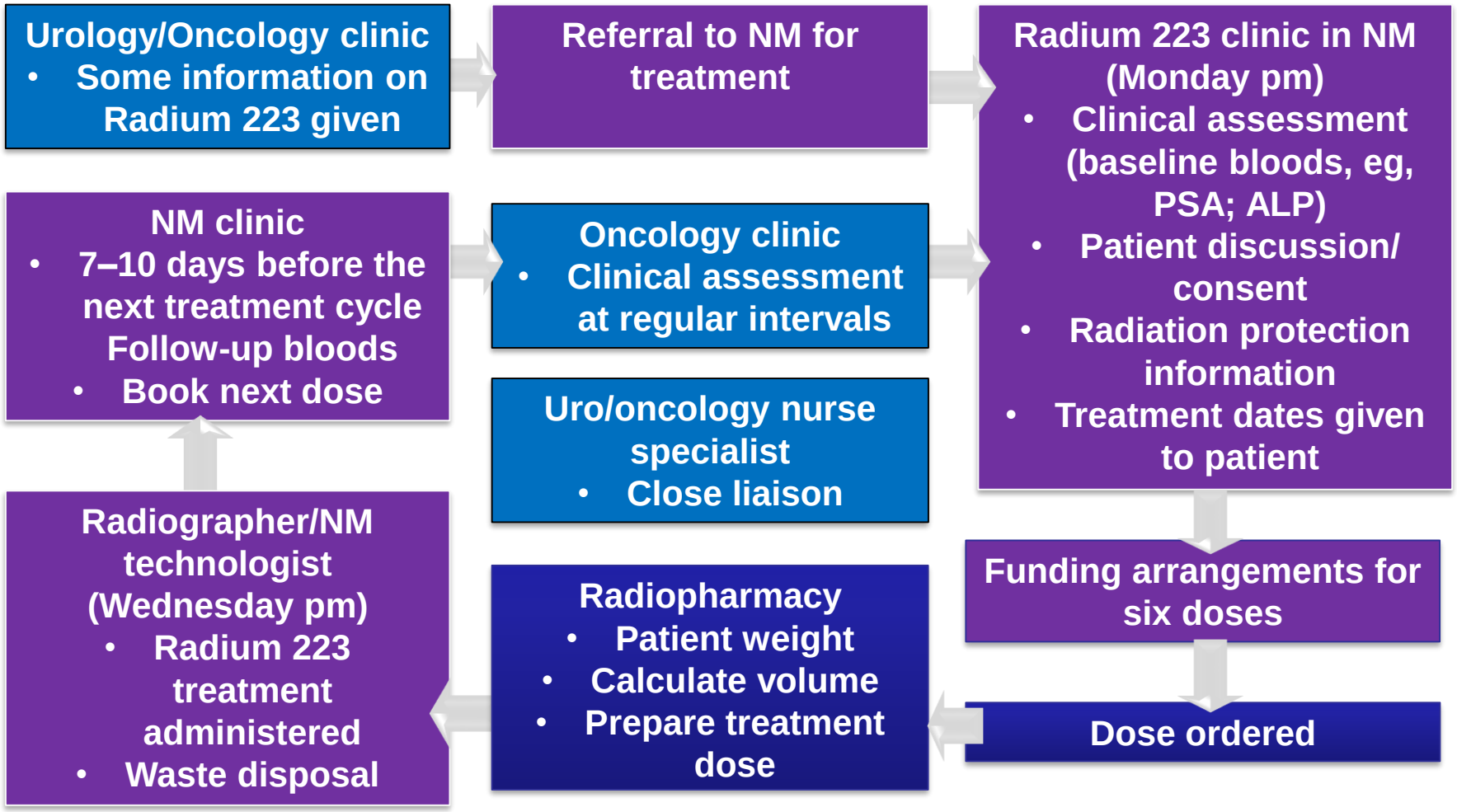
- Safe when combined with ADT and traditional hormonal therapy
- Safe when administered with EBRT
- Do not combine with abiraterone/prednisolone
- ERA 223 study : increased risk of fracture & death
- Enzalutamide : Ongoing PEACE III study
- Limited benefit to sequential abiraterone/enzalutamide
- Gene mutations lead to resistance to abi/enza
- Radium represents a logical alternative following progression on abiraterone/enzalutamide, rather than use of either of the hormonal agent

Radium 223 treatment aims



- Significant milestone in the treatment of mCRPC
- Embraced enthusiastically in NM communities worldwide

UHS Radium 223 patient pathway:



UHS Nuclear Medicine

Reference centre for radium-223 treatment in UK

Responsibilities for all tasks are distributed between different teams and three key staff members: nuclear medicine physician, advanced prostate cancer CNS and superintendent radiographer

Nuclear physician

- Initial consultations (all patients)
- Follow-up consultations (external patients)
- Assessment of patient referrals
- Assessment of blood results
- Writing of doctors letters
- Administrative tasks

Advanced Prostate Cancer CNS

- Monitoring of patients PC disease
- Smoothing referral pathway (only inpatients)
- Initial consultations (all patients)
- Follow-up consultations (external patients)
- Pre-assessment patient calls
- Collection of external blood results

Superintendent Radiographer

- Monitoring of patients Xofigo treatment
- Pre-assessment patient calls
- Collection of external blood results
- Xofigo injection appointment coordination
- Radioprotection advice

Radiographer Team

- Xofigo injection
- Xofigo disposal

Admin Team

- Xofigo order confirmation
- Xofigo injection appointments

Radiopharmacy Team

- Xofigo ordering
- Xofigo preparation
- Xofigo disposal

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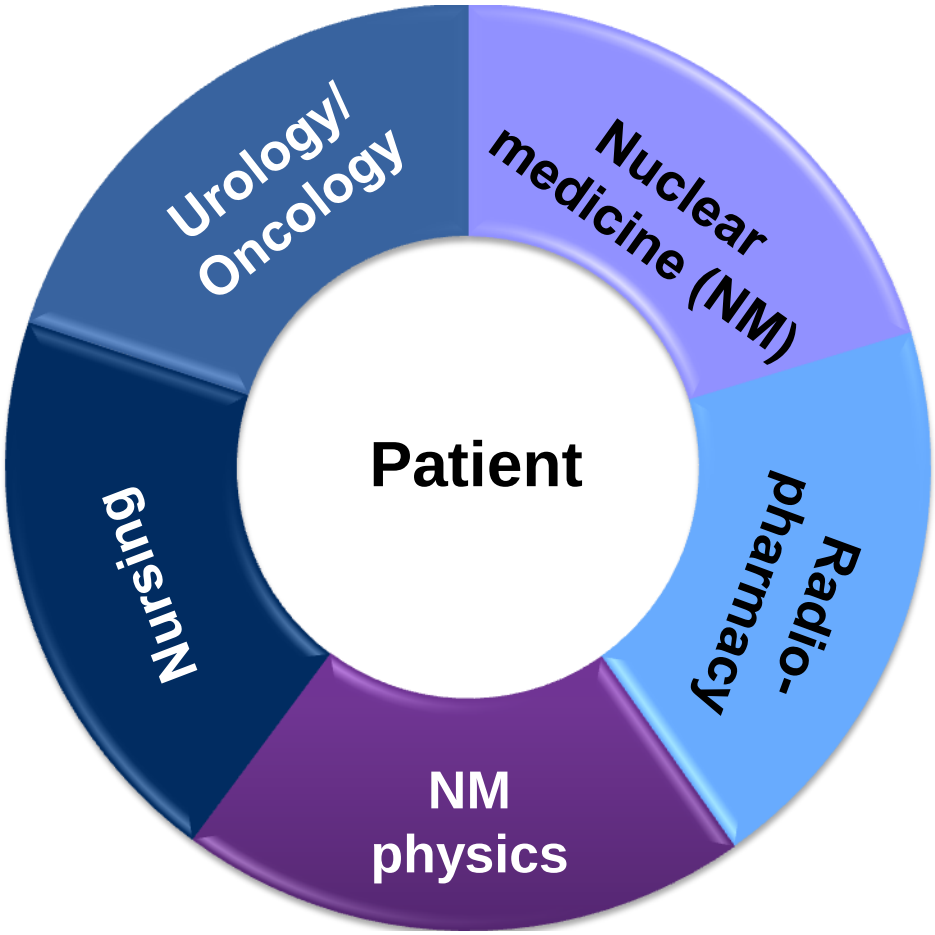
Weekly schedule of radium-223 related tasks

- **Radium related tasks are performed from Monday to Wednesday with injections on Tuesday and Wednesday.**

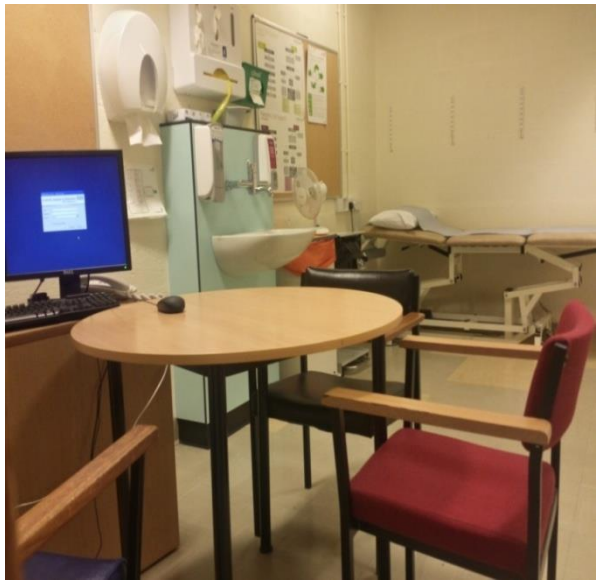
Monday	Tuesday	Wednesday	Thursday	Friday
Initial-/Follow-up consultations	Additional Xofigo therapy day	Main Xofigo therapy day	Patient clinical admin e.g clinic letters & blood results	Patient clinical admin e.g clinic letters & blood results
Xofigo ordering (for Tuesday therapy)	Xofigo ordering (for Wednesday therapy)	Patient review during therapy		
	Pre-therapy telephone clinic	Radium team meeting to discuss patients		

Radium 223 – collaboration within the multidisciplinary team (MDT)



Radium 223 treatment: teamwork

- Good organization between departments:
  - Senior staff member in NM and nurse specialists are key coordinators
- Close liaison within the MDT
- Identify which specialty will follow up with the patient:
  - NM physician can manage certain events
  - Refer to oncologist if there are more challenging events
  - Acute oncology service input available 24/7
  - Role of clinical nurse specialist to coordinate aspects of patient care
- Clear information for patients provides reassurance
- Suitable patient facility in clinic



Radium 223 care plan

Date of Clinic Visit :

Cycle 1
Therapy date

Nuclear Medicine Nurse/Radiographer/Technologist	Notes	Signature (Print Name)
Ask patient whether their clinical condition has changed post clinic visit (if yes refer to Consultant/Radiographer responsible for the patient)		
Check blood results if HB <10g/dL Neutrophil < 1.5x10⁹/L Platelet count < 50x10⁹/L Refer to Consultant/Radiographer responsible for patient Actual HB Actual Neutrophil Actual Platelet count	Date of sample	
Cannulate patient		
Administer therapy as per administration protocol		
Give patient's radiation protection restrictions sheet		
Dispose of syringes/cannula/gloves in appropriately marked sharps bin.		
Monitor room for contamination		
Record administration on CRIS and Isostock		

Pre-treatment clinic visit 2nd cycle

Date & Time	Consultant/ Radiographer	Notes	Signature (Print Name)
	Discuss side effects from last therapy (if significant discuss with Consultant)		
	Discuss patient clinical condition since last therapy(if significant discuss with Consultant)		
	Discuss radiation protection restrictions.		
	Height and weight to be recorded		
	Give patient blood forms for FBC		
	Continence		
	Inform patient of proposed date of treatment		
	Ensure patient has contact phone numbers for nurse specialist and Acute Oncology Service (AOS)		
	Document clinic visit on eDOCS		

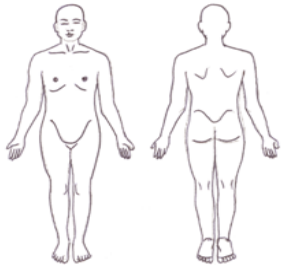
Pre-treatment clinic visit

Date	Consultant	Notes	Signature

Clinical Notes:

Height: .....cms **Weight:** .....kg **Date:** / /

Please mark areas of pain



Xofigo Therapy Information Sheet

Nuclear Medicine
University Hospital Southampton
Tremona Road
Southampton
SO16 6YD
Tel 023 8120 6203 Fax 023 8120 6927

Affix Patient Label Here
PID PID

Radionuclide	Ra-223
Activity (kBq)	3500
Administered on	15/09/2014 by Mrs Sandra Johns
ARSAC Holder responsible for treatment	Dr Francis Sundram
These restrictions have been explained by	Mrs Sandra Johns

Please carry this card with you at all times for **one week** following treatment

If you require dental or medical attention in this time period, please show this card to clinical staff as soon as possible

Please keep this card with your passport for the next **three months** when travelling through airports, ports or international railway stations (e.g. Eurostar)

Please avoid fathering a child for 6 months

Please follow the advice below:-

Do not return to work:	No Restriction
Sleep separately from your partner (beds at least 2m / 6 feet apart):	No Restriction
Avoid long journeys (+2 hrs) on public transport:	No Restriction
Avoid social events, cinema, restaurants:	No Restriction

Please Minimise Repeated/Prolonged Contact Time at Close Distances until:-

Adults	No Restriction
Children over 5 years:	No Restriction
Children under 5 years (Visiting):	**For 1 Day** following treatment*
Pregnant Women (Visiting):	**For 1 Day** following treatment*
Children under 5 years Staying at Home:	**For 1 Week** following treatment*
Pregnant Women Staying at Home:	**For 1 Week** following treatment*

** Local advice to minimise possible exposure to young children, babies & pregnant women*

Pay particular attention to good hygiene practice during the next week-
Flush the toilet twice each time you go un Monday 22/09/2014

In an emergency please contact the Acute Oncology Service (AOS) at Southampton on 07867 973 649, available 24 hours a day

Patient Radiation Restrictions Sheet

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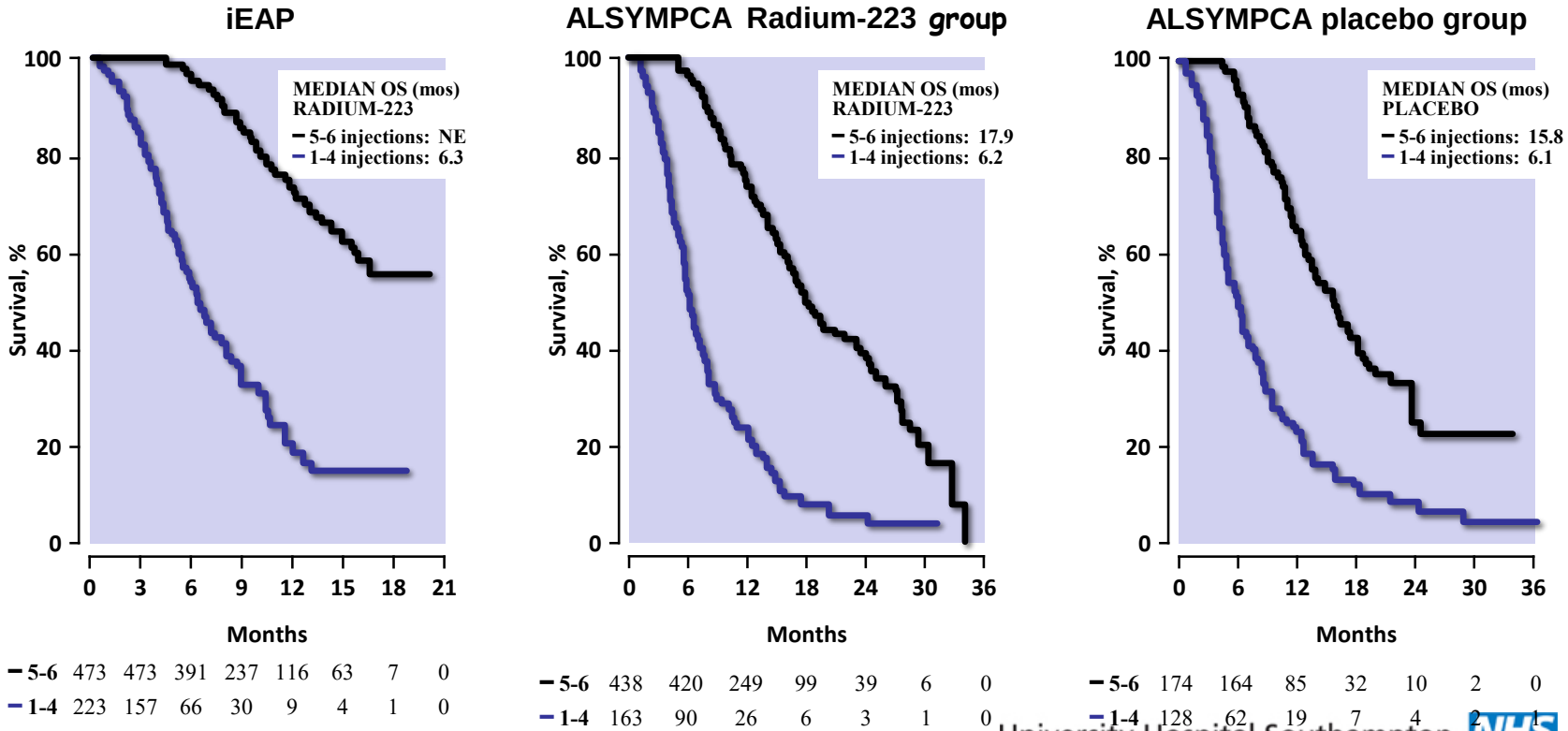
WESSEX NET GROUP

ENETS Centre of Excellence

Radium-223 efficacy: OS by number of injections

- ALSYMPCA: longer median OS with 5-6 injections of Radium-223 vs 5-6 injections of placebo
- iEAP and ALSYMPCA (Radium-223 group): longer median OS with 5-6 vs 1-4 injections



NE = not estimable.

SOURCE: Saad F, et al. *J Clin Oncol.* 34, 2016 (suppl; abstr 5082).

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Radium 223 treatment monitoring in clinical practice

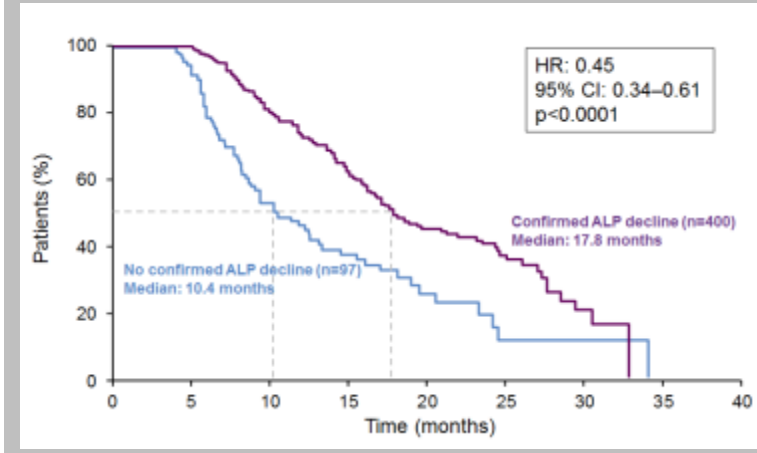
- PSA response may or may not be seen, and is not expected based on mechanism of action of Radium 223
- Treatment should not be discontinued based on PSA
- Cautious interpretation in first 2-3 months after starting treatment
- PSA flare following start of chemotherapy & novel hormonal agents
- PSA alone is not reliable enough for CRPC disease monitoring eg. visceral metastases may develop in men without rising PSA
- PSA response in ALSYMPCA:

	Radium 223	Placebo	*p* value
≥30% reduction in PSA blood levels at week 12 (%)	16	6	<0.001
≥30% reduction in PSA blood levels sustained through end of treatment (4 weeks after last injection) (%)	14	4	<0.001

Radium 223 treatment monitoring in clinical practice

- ALP can be monitored but treatment should not be discontinued based on ALP
- Majority of patient receiving radium-223 have an ALP decrease
- Potential biomarker to monitor treatment

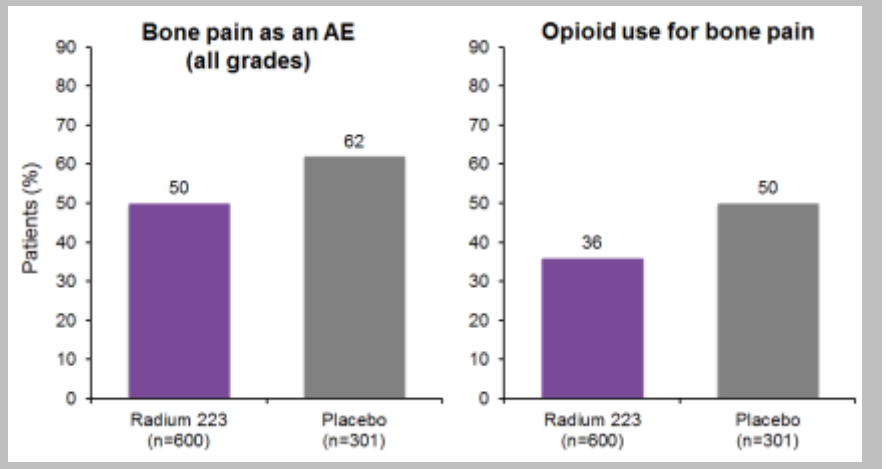
Overall survival by confirmed ALP decline at Week 12 (Radium 223 group, ALSYMPCA)



Radium 223 treatment monitoring in clinical practice

- Pain response may or may not be seen
- Not adequate to monitor treatment response by pain response
- Treatment should not be discontinued based on pain response
- Pain flare not uncommon (~5% of patients)
- Worsening pain may be due to degenerative disease or osteoporotic fracture

ALSYMPCA post hoc analysis of bone pain



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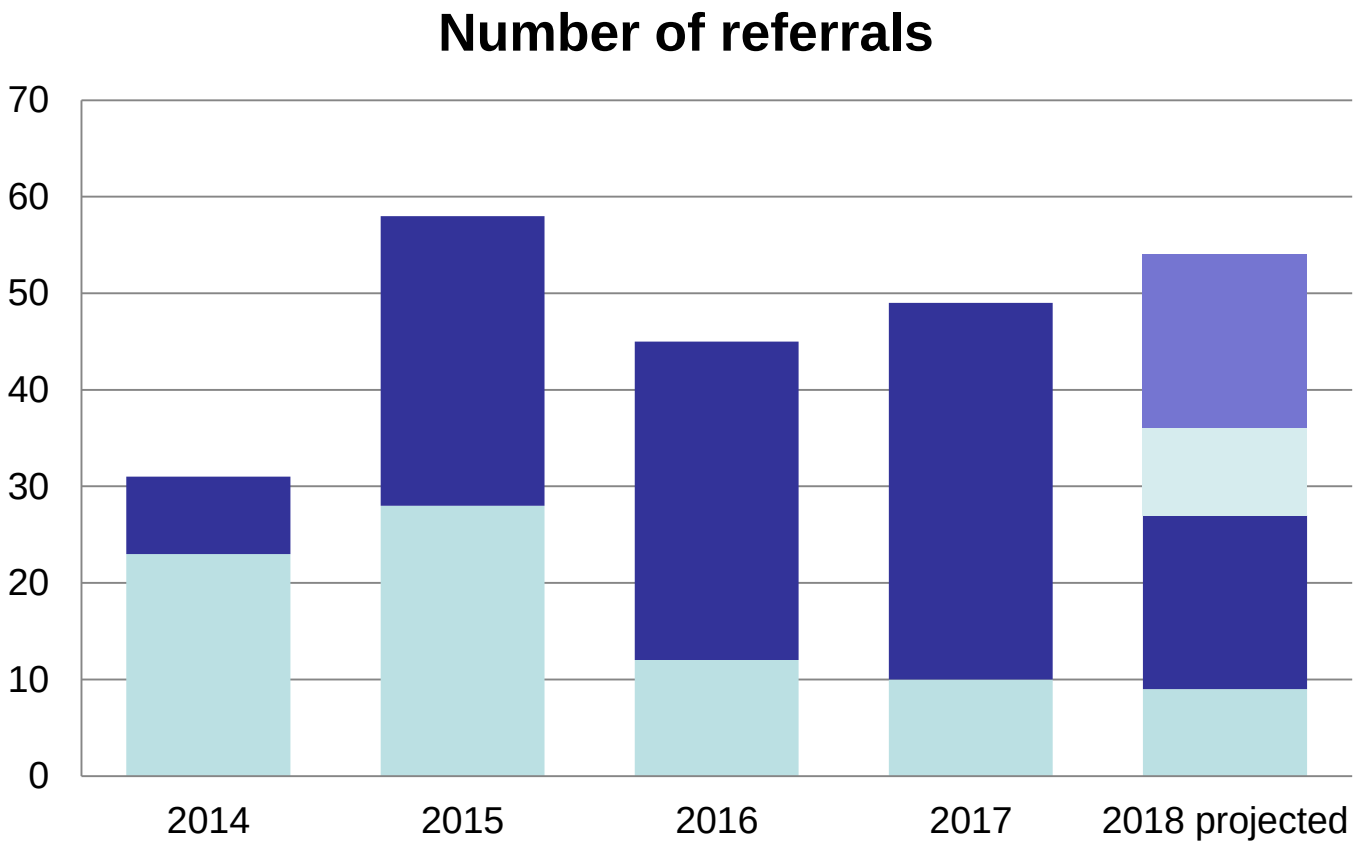
UHS Radium-223 therapy experience

- In ~ 4 years (Mar 14 – July 18)
  - 210 patients referred for Ra-223 therapy
  - 789 treatments administered
- Review of 21 month period (Mar 14 – Dec 15)
- 87 patients referred
  - 51 (59%) local and 36 (41%) external patients
- Mean age 72.3 yrs (range 54 -91 yrs)
- Mean performance status was 1.5
- 61 (70%) experienced bone pain; 50 (57 %) were on analgesia

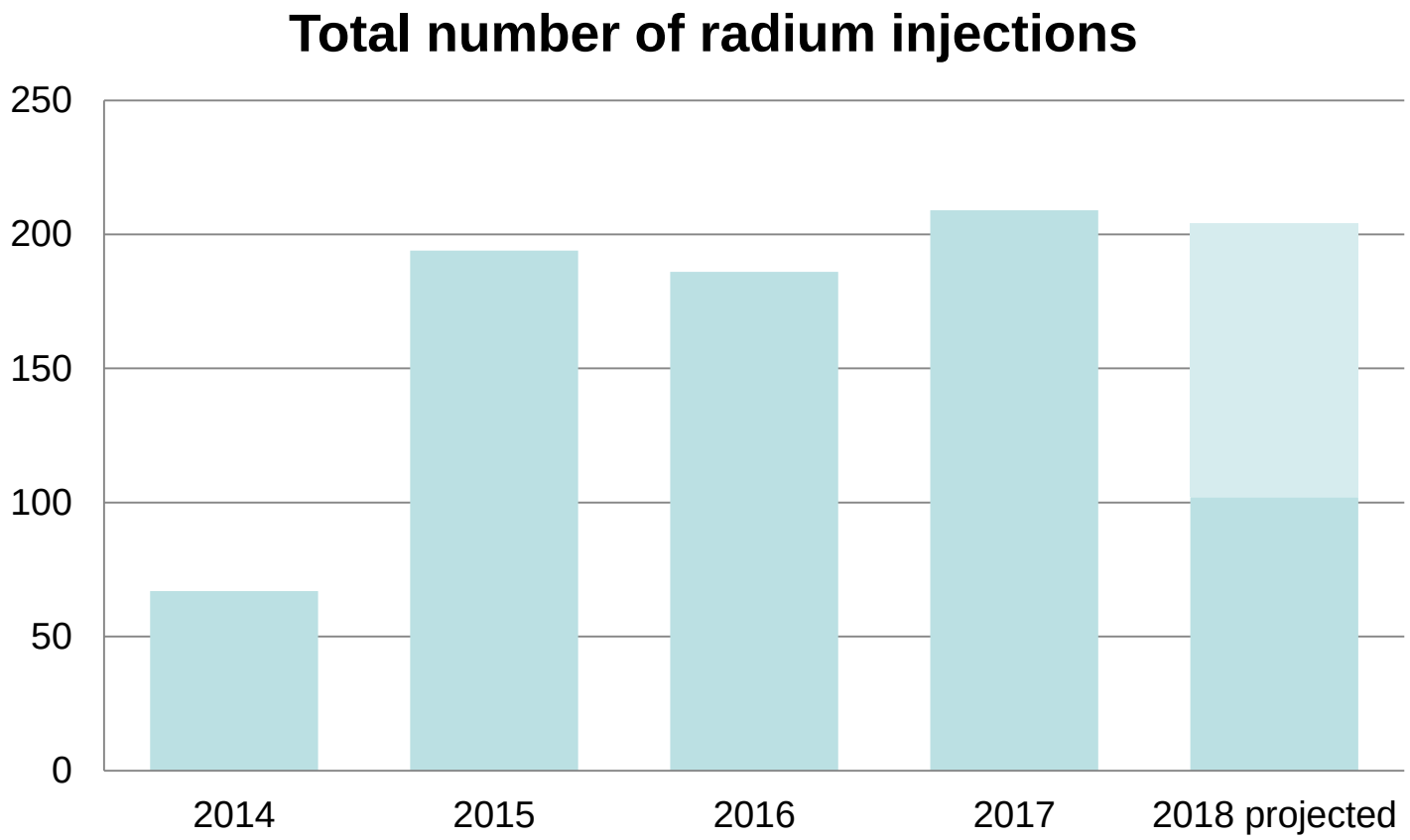
UHS Radium-223 therapy experience

- All patients had prior hormonal therapy:
  - 31 (36%) had prior chemotherapy
  - 20 (23%) had other prior therapies
- 21 (24%) did not commence treatment as they were unsuitable or had progressed.
- Of 66 (76%) who commenced treatment:
  - 25 (38%) completed the recommended 6 cycles
  - 18 (27%) remain on treatment
  - 23 (35%) discontinued treatment due to clinical deterioration or progressive disease

UHS Radium-223 therapy experience



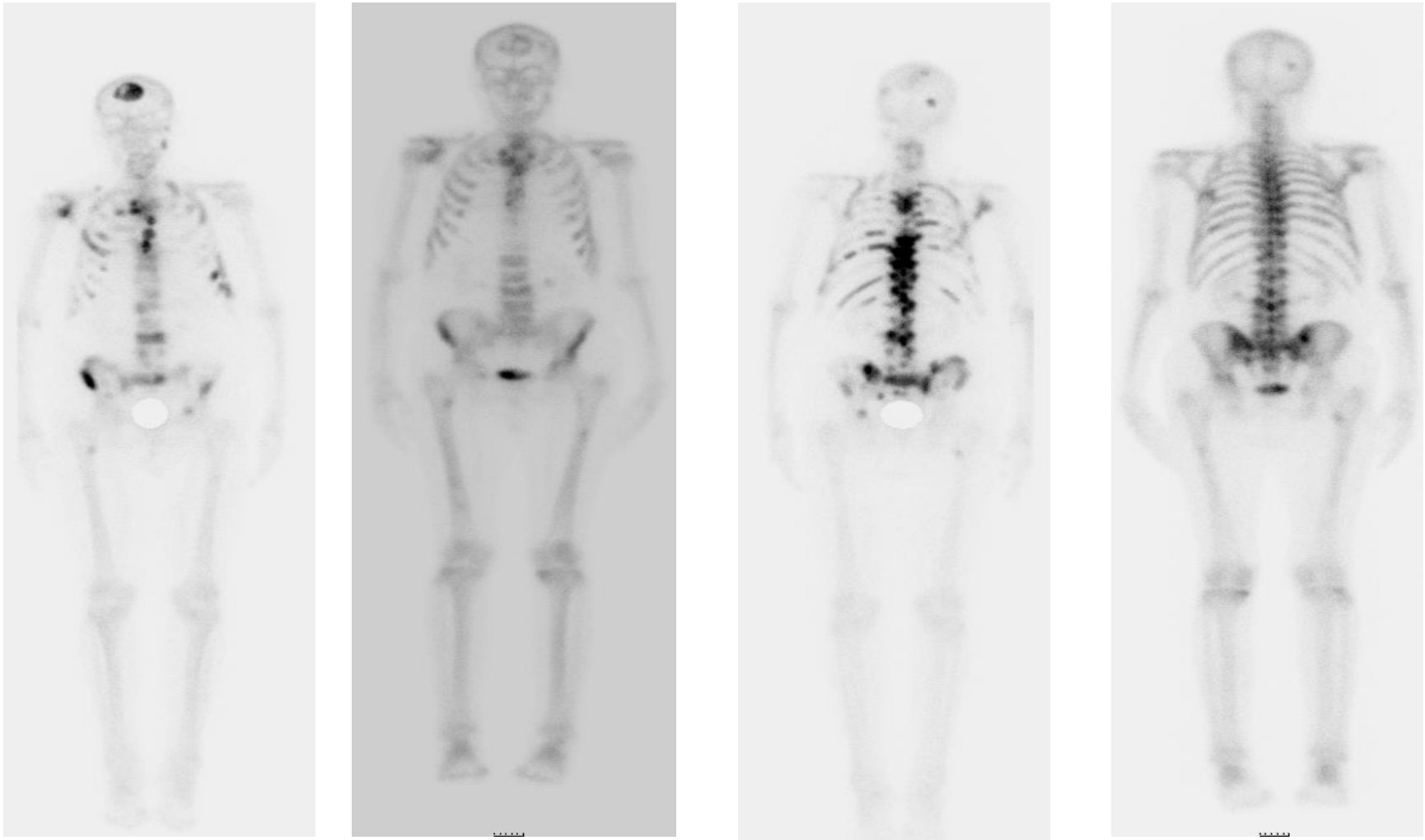
UHS Radium-223 therapy experience



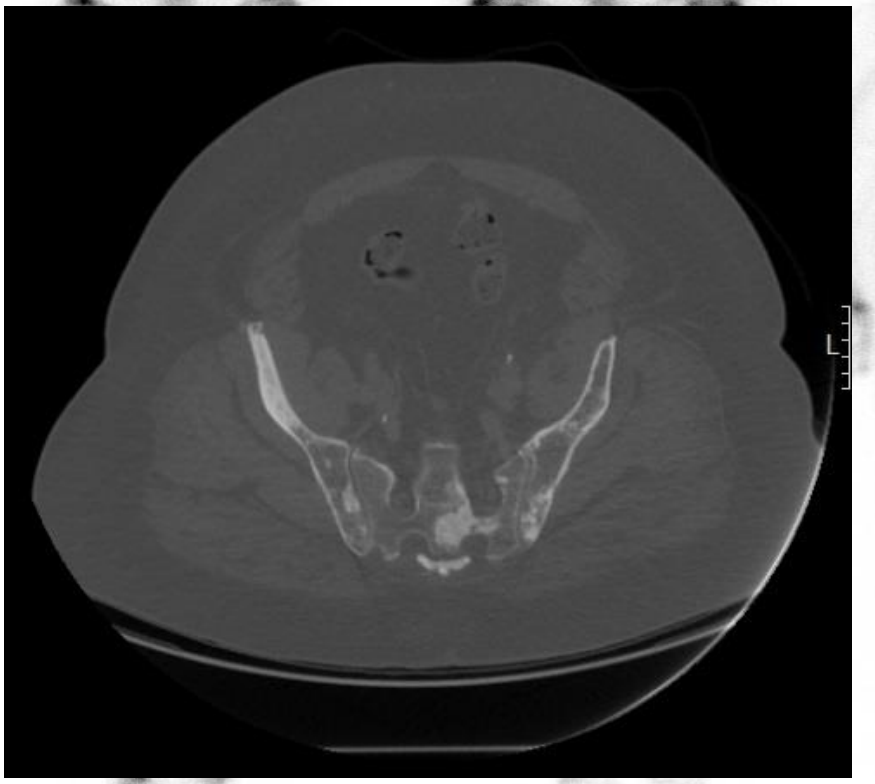
Patient case study 1 : Radium 223 therapy

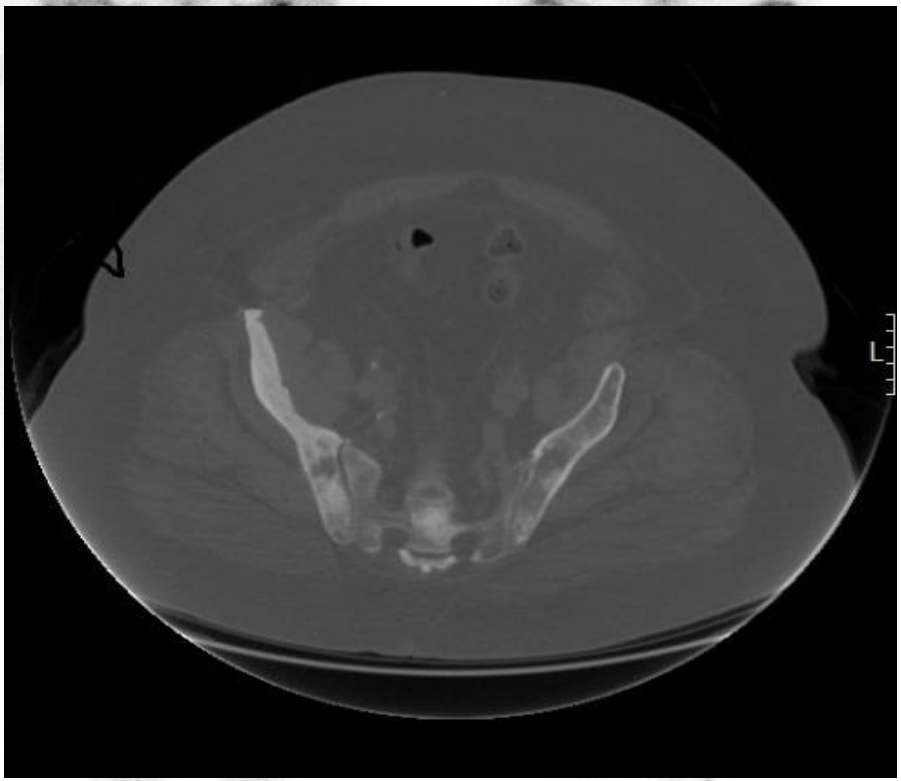
- 2000 – diagnosed with prostate Ca, radical RT. Previous palliative RT, MAB and Abiraterone
- Pre treatment: pain score 10, PS 2, fentanyl patch
- Jul – Dec 15: 6 cycles Radium-223
- Post treatment: pain score 1, PS 0, going to gym, no pain killers
- PSA fall : 131 → 60. ALP fall : 518 → 136
- Very good clinical response to treatment:
  - Excellent pain relief
  - “Hugely better, mood much improved”
- Bone scan shows….

Bone scans pre & post treatment



Bone and CT scans pre & post treatment





Ra-223: Pivotal role of Nuclear Medicine

- Paradigm shift in the role of therapeutic NM in the prostate cancer landscape:

  - beyond imaging and diagnostic support

  - from bone pain palliation to front-line therapy in mCRPC

  - requires active NM specialist involvement as integral member of the prostate MDT

- Vital to understand clinical profile and where it sits in the treatment algorithm in order to optimize clinical utility
- Effective interaction with radiation safety authorities:

  - to ensure that local policies reflect the low risk profile of this life-prolonging therapy

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ORIGINAL ARTICLE

Practical recommendations for radium-223 treatment of metastatic castration-resistant prostate cancer

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Abstract

Purpose Radium Ra 223 dichloride (radium-223, Xofigo®) is the first targeted alpha therapy for patients with castration-resistant prostate cancer and symptomatic bone metastases. Radium-223 provides a new treatment option for this setting, but also necessitates a new treatment management approach. We provide straightforward and practical recommendations for European nuclear medicine centres to optimize radium-223 service provision.

Methods An independent research consultancy agency observed radium-223 procedures and conducted interviews with all key staff members involved in radium-223 treatment delivery in 11 nuclear medicine centres across six countries (Germany, Italy, the Netherlands, Spain, Switzerland and the UK) experienced in administering radium-223. The findings were collated and discussed at a meeting of experts from these centres, during which key consensus recommendations were defined.

Results The recommendations cover centre organization and preparation; patient referral; radium-223 ordering, preparation and disposal; radium-223 treatment delivery/administration; and patient experience. Guidance includes structured coordination and communication within centres and multidisciplinary teams, focusing on sharing best practice to provide high-quality, patient-centred care throughout the treatment pathway.

Conclusions These expert recommendations are intended to complement existing management guidelines. Sharing best practice and experience will help nuclear medicine centres to optimize radium-223 service provision and improve patient

Radium-223 in CRPC guidelines

Radium-223 indication	Treatment of adults with CRPC, symptomatic bone metastases and no known visceral metastases
ASCO/CCO 2014	Radium-223 treatment should be offered to men with bone metastases
ESMO 2015	Radium-223 is recommended for bone-predominant symptomatic mCRPC without visceral metastases
NCCN 2016	Radium-223 for symptomatic bone metastases and no visceral metastases (1st-line use and after systemic therapy)
EAU 2018	Treat patients with mCRPC with life-prolonging agents. Choose 1st-line treatment based on PS, symptoms, comorbidities, and extent of disease (*abiraterone, docetaxel, enzalutamide, radium-223, sipuleucel-T) In patients with mCRPC and progression following docetaxel chemotherapy offer further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide and radium-223

MRT at UHS Nuclear Medicine Department

- **Aim: To be one of the leading MRT centres in the UK**