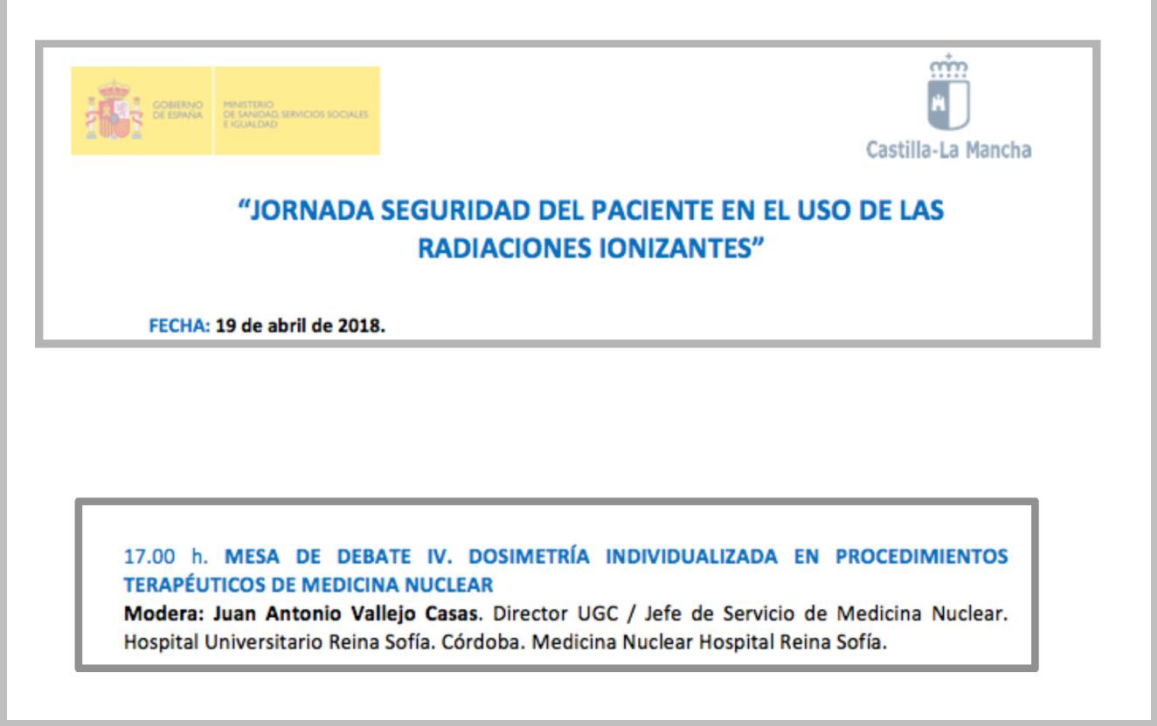

Dosimetría en emisiones alfa y expectativas de futuro

J. CASTELL

Medicina Nuclear

HOSPITAL UNIVERSITARI VALL D'HEBRON

Barcelona

DIRECTIVA 2013/59/EURATOM DEL CONSEJO

de 5 de diciembre de 2013

por la que se establecen normas de seguridad básicas para la protección contra los peligros derivados de la exposición a radiaciones ionizantes, y se derogan las Directivas 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom y 2003/122/Euratom

1. Los Estados miembros velarán por que todas las dosis debidas a exposiciones médicas con fines de diagnóstico radiológico, radiología intervencionista, planificación, guía y verificación se mantengan lo más bajas que sea razonablemente posible, para que pueda obtenerse la información médica requerida, teniendo en cuenta factores sociales y económicos.

Para todas las exposiciones médicas de pacientes con fines radioterapéuticos, las exposiciones del volumen blanco se planificarán individualmente y se verificará convenientemente su realización, teniendo en cuenta que las dosis de los volúmenes y tejidos fuera del blanco deberán ser lo más bajas que sea razonablemente posible y estarán de acuerdo con el fin radioterapéutico deseado de la exposición.

GUIÓN

PRINCIPIOS DE LA TERAPIA CON RADIONÚCLIDOS

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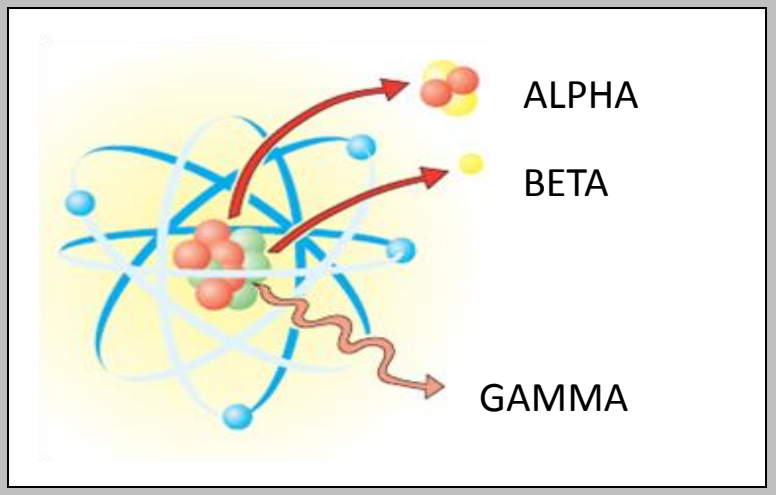
PERSPECTIVAS DE FUTURO DE LA TERAPIA CON RN ALFA

EMISSION TYPES OF UNSEALED RADIOACTIVE SOURCES



RADIACTIVE EMISSION:

Alpha: 2p + 2n (He)

Beta: e^+, e^-

Particles - TREATMENT

Gamma

X

Electromagnetic - IMAGE

RADIOFÁRMACO

RADIONÚCLIDO + **VECTOR**

Átomo*

Molécula*

Célula*

UNIÓN ESPECÍFICA A LA DIANA BIOLÓGICA

Diseñado según el proceso metabólico a diagnosticar o tratar

REAL DECRETO 479/1993, DE 2 ABRIL. REGULA LOS MEDICAMENTOS RADIOFÁRMACOS DE USO HUMANO
(BOE núm. 109, de 7 mayo)

Los radiofármacos son medicamentos que han adquirido gran importancia en la práctica clínica por su aplicación con finalidades tanto terapéuticas como diagnósticas.

Los radiofármacos son medicamentos

Su introducción en la práctica clínica sigue los mismos procedimientos que los otros medicamentos

Fase preclínica

Ensayos clínicos

- Fase I: Biodistribución, farmacocinética, seguridad. Determinación de la dosis
- Fase II: Farmaco-dinámica, establecer la relación dosis-respuesta
- Fase III (regulatoria): Evaluación de la eficacia y seguridad terapéutica

MINISTERIO
DE SANIDAD, SERVICIOS SOCIALES
E IGUALDAD

agencia española de
medicamentos y
productos sanitarios

INFORME DE POSICIONAMIENTO TERAPÉUTICO
PT/V1/02032015

Informe de Posicionamiento Terapéutico de radio-223 (^{223}Ra) (Xofigo®)

ANEXO I

FICHA TÉCNICA O RESUMEN DE LAS CARACTERÍSTICAS DEL PRODUCTO

3. FORMA FARMACÉUTICA

Vall d'Hebron
Barcelona Campus Hospitalari

Solución inyectable.

Solución isotónica, transparente e incolora, con un pH comprendido entre 6,0 y 8,0.

4. DATOS CLÍNICOS

4.1 Indicaciones terapéuticas

Xofigo está indicado para el tratamiento de adultos con cáncer de próstata resistente a la castración, con metástasis óseas sintomáticas y sin metástasis viscerales conocidas.

4.2 Posología y forma de administración

Xofigo debe ser administrado únicamente por personas autorizadas para manejar radiofármacos en entornos clínicos designados (ver sección 6.6) y tras la evaluación del paciente por un médico cualificado.

Posología

La pauta posológica de Xofigo es de una actividad de 55 kBq por kg de peso corporal, administrados en intervalos de 4 semanas hasta completar 6 inyecciones.

No se ha estudiado la seguridad y eficacia de más de 6 inyecciones de Xofigo.

Para información detallada sobre el cálculo del volumen que se debe administrar, ver sección 12.

Edad avanzada
En términos generales no se observaron diferencias en la seguridad o eficacia entre los pacientes de edad avanzada (≥ 65 años) y los de edades más jóvenes (< 65 años) en el estudio de fase III.
No se considera necesario ajustar la dosis en los pacientes de edad avanzada.

Insuficiencia hepática
No se ha estudiado la seguridad y eficacia de Xofigo en los pacientes con insuficiencia hepática.
Dado que el radio-223 no se metaboliza en el hígado ni se elimina por vía biliar, no se prevé que la insuficiencia hepática afecte a la farmacocinética del dicloruro de radio-223.
No se considera necesario ajustar la dosis en los pacientes con insuficiencia hepática.

Insuficiencia renal
En el estudio clínico de fase III, no se observaron diferencias relevantes en cuanto a seguridad o eficacia entre los pacientes con insuficiencia renal leve (aclaramiento de creatinina [CLCR]: 50 a 80 ml/min) y los de función renal normal. Se dispone de datos limitados para los pacientes con insuficiencia renal moderada (CLCR: 30 a 50 ml/min). No se dispone de datos para los pacientes con insuficiencia renal grave (CLCR < 30 ml/min) o nefropatía terminal.
No obstante, dado que la excreción urinaria es mínima y la principal vía de eliminación son las heces, no se prevé que la insuficiencia renal afecte a la farmacocinética del dicloruro de radio-223.
No se considera necesario ajustar la dosis en los pacientes con insuficiencia renal.

Población pediátrica
No se ha estudiado la seguridad y eficacia de Xofigo en niños y adolescentes menores de 18 años. No existe

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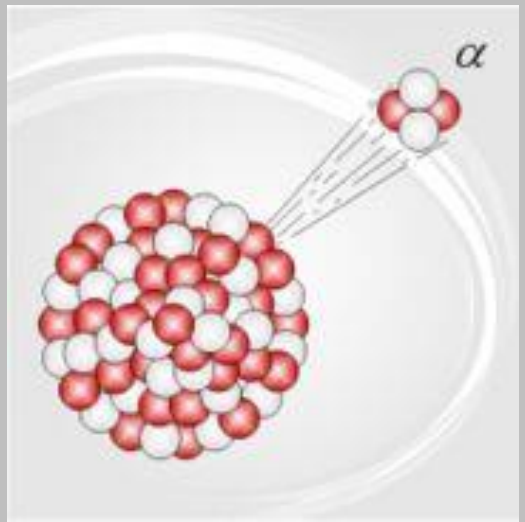
Principles of Radionuclide Treatment

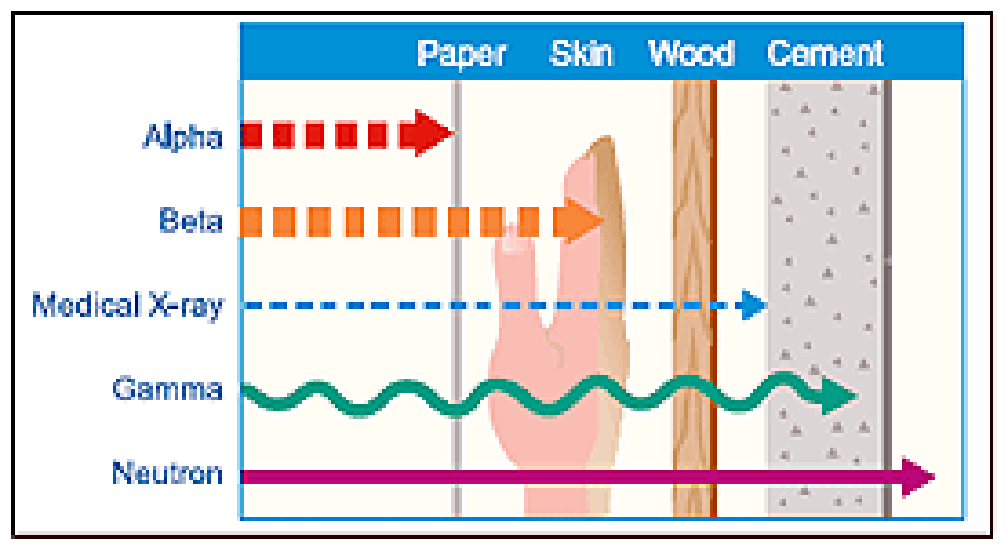
- Optimal half-life of the radionuclide
- Decay tipe
- Particle characteristics
- Linear energy transfer coefficient (LET)
- Relative biological effectiveness (RBE)
- High affinity with the target
- Low irradiation to healthy tissues
- Pharmacodynamics adjusted to the desired dosimetry

ALPHA EMISSION

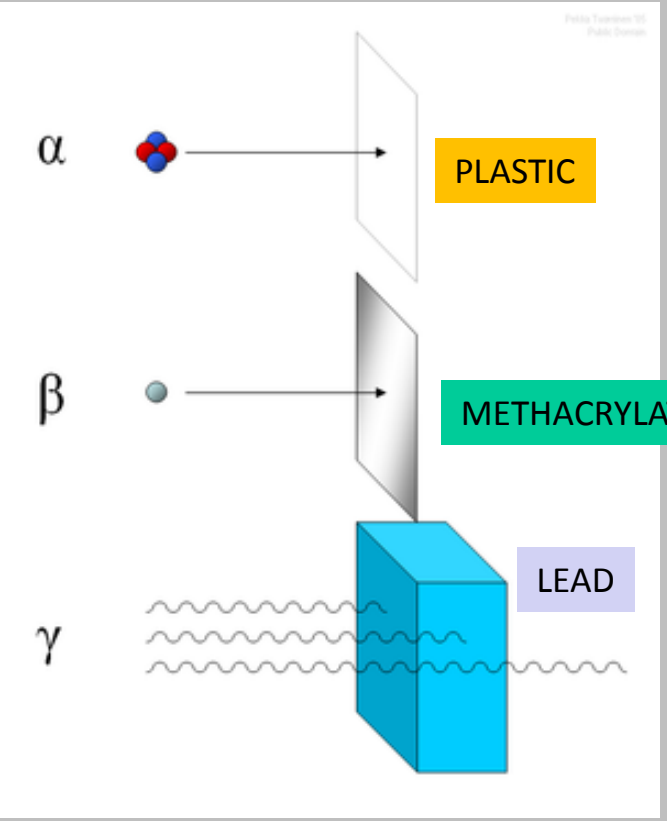
- High energy heavy helium nuclei
- 2 protons + 2 neutrons (^4He)



RADIATION PENETRATION



REQUIRED SHIELDING

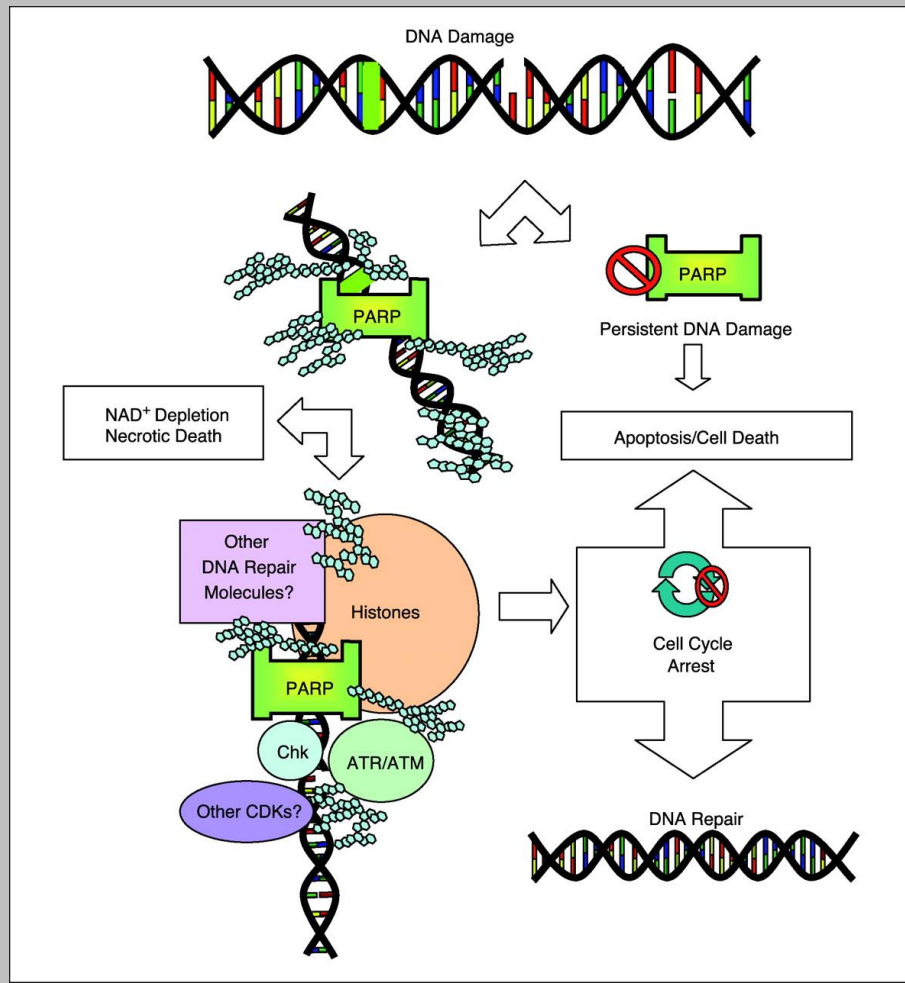


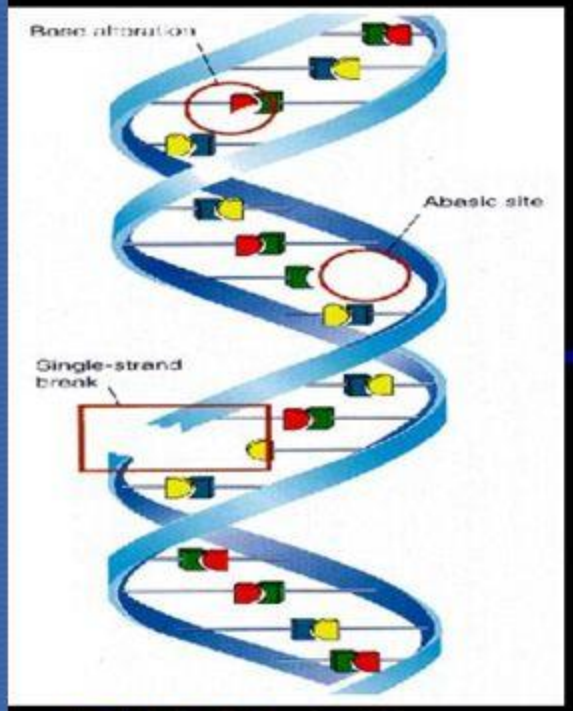
Therapeutic Advantages of Alpha Particles

- Very short trajectory in delivering virtually all its energy (40-80 mm), high Linear Energy Transfer between 5 and 8 Mev)
- An alpha particle traversing a cellular core of 0,1 mm in diameter, deliver a 800 keV energy equivalent to a dose of approximately 0.25 Gy
- High RBE of such radiation allows inactivation of exposed cells with few particles in contrast to gamma radiation or beta particles

Biologic effect

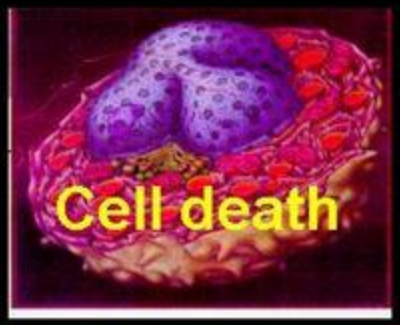
- Output electrons of the atomic shell
- Appearance of ions and free radicals
- DNA molecular changes
  - Chromosomal damage
  - Cell growth disorder
  - Apoptosis
  - Cell death





DNA Mutation

Viable Cell



Unviable Cell

Cancer ?

IAEA

GUIÓN

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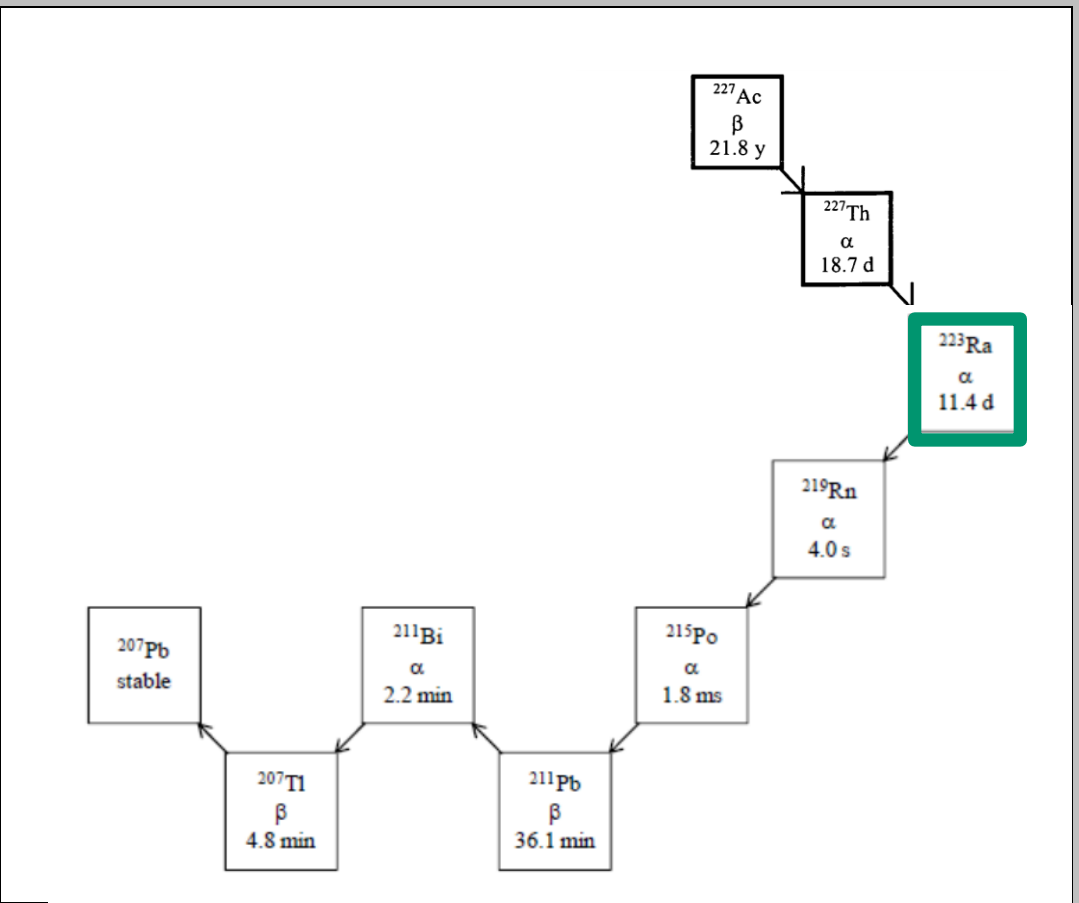
Radium-223

Alpha particle-emitter with a half-life of 11.4 days
The specific activity of radium-223 is 1.9 MBq/ng
Half-life 11.4 days
Actinium-227 is produced by neutron irradiation of natural ^{226}Ra.



Purified ^{227}Ac comes into equilibrium with its decay products (^{227}Th and ^{223}Fr) after 185 days

No traces found in Ra-223 vials!!

alpha-particles 95.3%
5.0 - 7.5 MeV

β -particles 3.6%
0.445 MeV - 0.492 MeV

γ radiation <2%
269 keV, 154 keV, 324 keV

PRECLINICAL STUDIES

Animal data and dosimetric estimates have indicated that bone-targeted a-emitters can deliver therapeutic relevant radiation doses to bone surfaces and skeletal metastases at activity levels that should be acceptable in terms of bone marrow radiation exposure

Therapeutic study of ^{223}Ra in a nude rat skeletal metastases model showed a significant antitumor activity

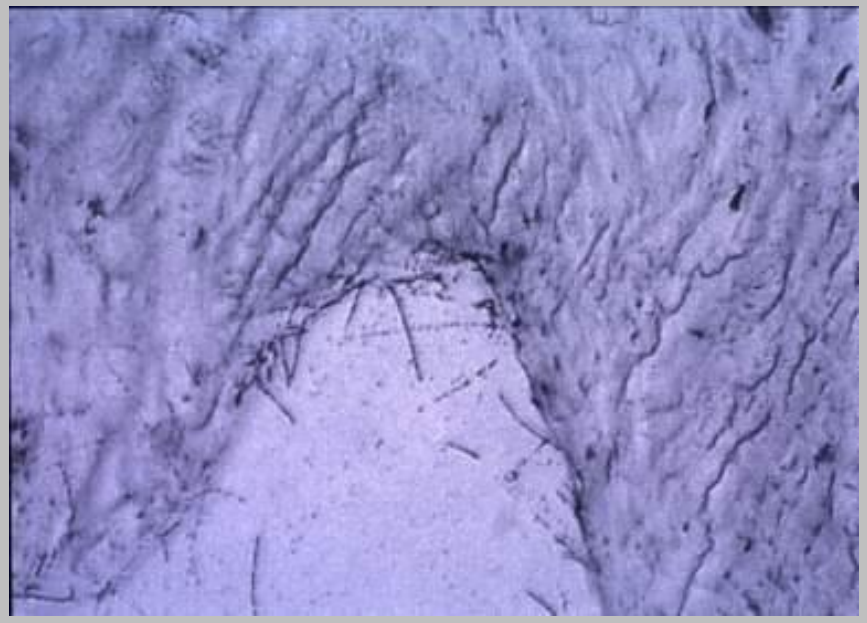
Biodistribution study of ^{223}Ra in a dog with bone cancer showed affinity for and stability within calcified tissues. Radium-223, eliminated via intestinal clearance, resided in transit in the gut content, whereas the activity in intestinal walls was low and comparable with the other soft tissues.

a-Track microautoradiography of canine specimens indicated a concentration of bone-seeking a-emitter on the bone surfaces of trabecular bone in a vertebra and a very high accumulation in strongly osteoblastic bone matrix

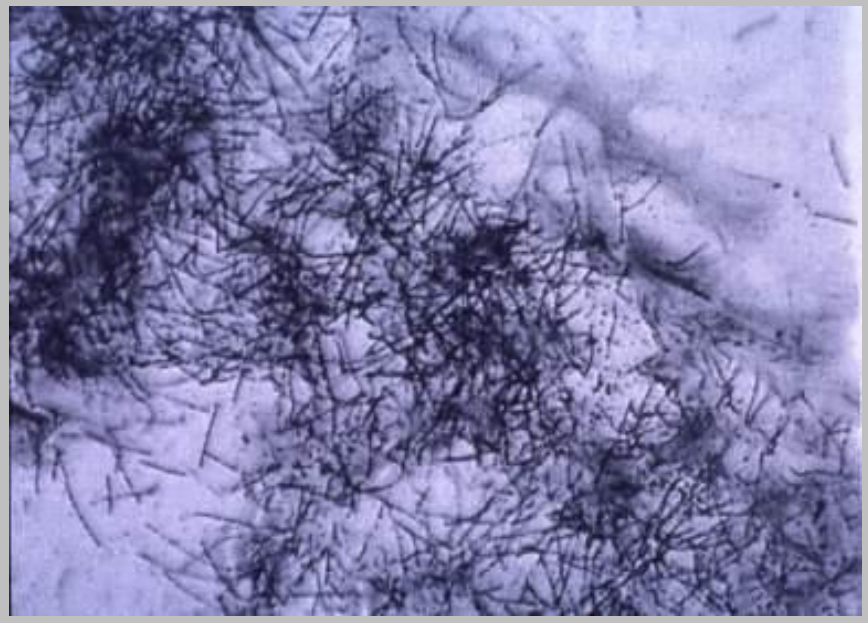
High-Linear EnergyTransfer IrradiationTargeted to Skeletal Metastases by the A-Emitter 223Ra: Adjuvant or Alternative to ConventionalModalities? Bruland OS, Clin Cancer Res 2006

Radium-223 ($^{223}RaCl_2$)

Bone microautoradiography of dogs after injection ^{223}Ra
Distribution of particles in a normal bone and in increased osteoblastic area



normal spongious bone



osteoblastic zone

OS Brulant et al, Clin Cancer Res 2006;12:6250s

Eur J Nucl Med Mol Imaging (2013) 40:1384–1393
DOI 10.1007/s00259-013-2427-6

ORIGINAL ARTICLE

Phase I pharmacokinetic and biodistribution study with escalating doses of ^{223}Ra-dichloride in men with castration-resistant metastatic prostate cancer

Jorge A. Carrasquillo · Joseph A. O'Donoghue · Neeta Pandit-Taskar · John L. Humm · Dana E. Rathkopf · Susan F. Slovin · Matthew J. Williamson · Kristine Lacuna · Anne-Kirsti Aksnes · Steven M. Larson · Howard I. Scher · Michael J. Morris

Target: Hydroxylapatite $(Ca_{10}(PO_4)_6(OH)_2)$

40-60% administered dose located in the skeleton

Increasing uptake until 24h

Low extraskeletal redistribution

Reduced bone marrow irradiation

Effective radiation in multiple locations

Effective radiation of micrometastases

High-Linear EnergyTransfer IrradiationTargeted to Skeletal Metastases by the A-Emitter 223Ra: Adjuvant or Alternative to Conventional Modalities?

Bruland OS, Clin Cancer Res 2006

Table 2. Summary of effective energy and dose constants for radium-223 and progeny for all emission combined

Nuclide	Effective energy*	Dose constant Δ (Gy kg/Bq/s)
^{223}Ra (11.43 d)	5.99	9.58×10^{-13}
	5.56†	8.90×10^{-13}
^{219}Rn (3.96 s)	6.95	1.11×10^{-12}
	6.72†	1.08×10^{-12}
^{215}Po (1.78 ms)	7.53	1.20×10^{-12}
	7.39†	1.18×10^{-12}
^{211}Pb (36.1 min)	0.518	8.29×10^{-14}
^{211}Bi (2.17 min)	6.75	1.08×10^{-12}
	6.57†	1.05×10^{-12}
^{207}Tl (4.77 min)	0.494	7.90×10^{-14}
Total	28.2	4.5×10^{-12}
	26.4†	4.2×10^{-12}

NOTE: From Nuclide Explorer data sheets, Institute for Transuranium Elements, Karlsruhe, Germany. European Commission, Joint Research Centre, Program Version 1.00 (1999). Branching of <1% is not considered.

*Includes α, β, photon, X-ray, and electron energies.

†Includes only α-particle energies.

Table 3. Estimated equivalent dose after i.v. injection of a dosage of 50 kBq/kg of ^{223}Ra

Target organs	Dose equivalents (Sv)
Adrenals	5.60×10^{-2}
Urinary bladder	5.70×10^{-2}
Brain	5.55×10^{-2}
Breast	5.55×10^{-2}
Gall bladder	5.60×10^{-2}
Heart wall	5.55×10^{-2}
Kidneys	5.60×10^{-2}
Liver	6.35×10^{-1}
Muscle	5.60×10^{-2}
Ovaries	5.65×10^{-2}
Pancreas	5.60×10^{-2}
Testes	5.55×10^{-2}
Thyroid	5.55×10^{-2}
Bone surface	13.05
Stomach	5.60×10^{-2}
Small intestine	5.65×10^{-2}
Upper large intestine	1.68×10^{-1}
Lower large intestine	3.67×10^{-1}
Skin	5.55×10^{-2}
Spleen	5.55×10^{-2}
Thymus	5.55×10^{-2}
Uterus	5.60×10^{-2}
Expiratory tract	5.55×10^{-2}
Lung	5.55×10^{-2}
Colon	2.54×10^{-1}
Thoracic lymph node	5.55×10^{-2}
Esophagus	5.55×10^{-2}
Gonads	5.65×10^{-2}
Remainder	5.60×10^{-2}

NOTE: The data represent ^{223}Ra in equilibrium with the daughter radionuclides and were calculated according to the ICRP-67 recycling model for radium. A quality factor of 5.0 for α particles was assumed.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 18, 2013 VOL. 369 NO. 3

Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

C. Parker, S. Nilsson, D. Heinrich, S.I. Helle, J.M. O'Sullivan, S.D. Fosså, A. Chodacki, P. Wiechno, J. Logue, M. Seke, A. Widmark, D.C. Johannessen, P. Hoskin, D. Bottomley, N.D. James, A. Solberg, I. Syndikus, J. Kliment, S. Wedel, S. Boehmer, M. Dall'Oglio, L. Franzén, R. Coleman, N.J. Vogelzang, C.G. O'Bryan-Tear, K. Staudacher, J. Garcia-Vargas, M. Shan, Ø.S. Bruland, and O. Sartor, for the ALSYMPCA Investigators*

ABSTRACT

BACKGROUND

Radium-223 dichloride (radium-223), an alpha emitter, selectively targets bone metastases with alpha particles. We assessed the efficacy and safety of radium-223 as compared with placebo, in addition to the best standard of care, in men with castration-resistant prostate cancer and bone metastases.

METHODS

In our phase 3, randomized, double-blind, placebo-controlled study, we randomly assigned 921 patients who had received, were not eligible to receive, or declined docetaxel, in a 2:1 ratio, to receive six injections of radium-223 (at a dose of 50 kBq per kilogram of body weight intravenously) or matching placebo; one injection was administered every 4 weeks. In addition, all patients received the best standard of care. The primary end point was overall survival. The main secondary efficacy end points included time to the first symptomatic skeletal event and various biochemical end points. A prespecified interim analysis, conducted when 314 deaths had occurred, assessed the effect of radium-223 versus placebo on survival. An updated analysis, when 528 deaths had occurred, was performed before crossover from placebo to radium-223.

RESULTS

At the interim analysis, which involved 809 patients, radium-223, as compared with placebo, significantly improved overall survival (median, 14.0 months vs. 11.2 months; hazard ratio, 0.70; 95% confidence interval [CI], 0.55 to 0.88; two-sided P=0.002). The updated analysis involving 921 patients confirmed the radium-223 survival benefit (median, 14.9 months vs. 11.3 months; hazard ratio, 0.70; 95% CI, 0.58 to 0.83; P<0.001). Assessments of all main secondary efficacy end points also showed a benefit of radium-233 as compared with placebo. Radium-223 was associated with low myelosuppression rates and fewer adverse events.

CONCLUSIONS

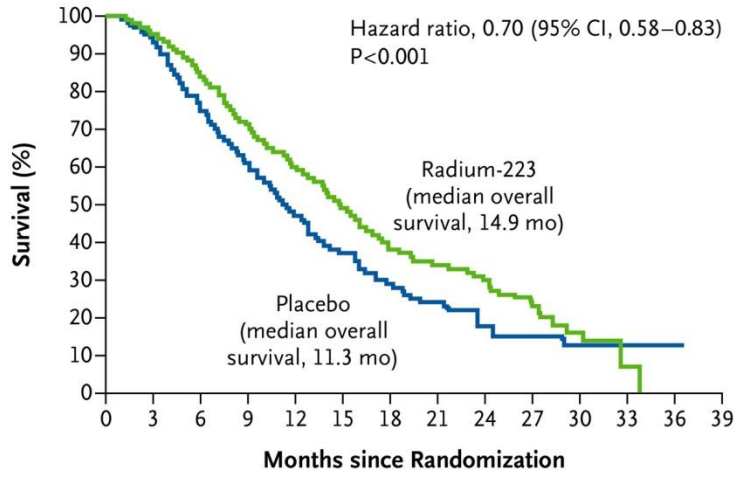
In this study, which was terminated for efficacy at the prespecified interim analysis, radium-223 improved overall survival. (Funded by Algeta and Bayer HealthCare Pharmaceuticals; ALSYMPCA ClinicalTrials.gov number, NCT00699751.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Parker at the Royal Marsden Hospital, Academic Urology Unit, Downs Rd., Sutton, Surrey SM2 5PT, United Kingdom, or at chris.parker@rmh.nhs.uk.

*Additional investigators in the Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) study are listed in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2013;369:213-23.
DOI: 10.1056/NEJMoa1213755

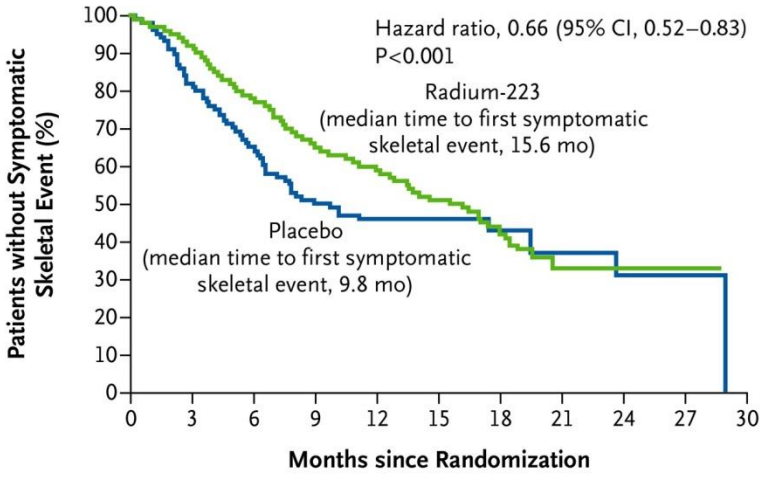
A Overall Survival



No. at Risk

Radium-223	614	578	504	369	274	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	103	67	39	24	14	7	4	2	1	0

B Time to First Symptomatic Skeletal Event



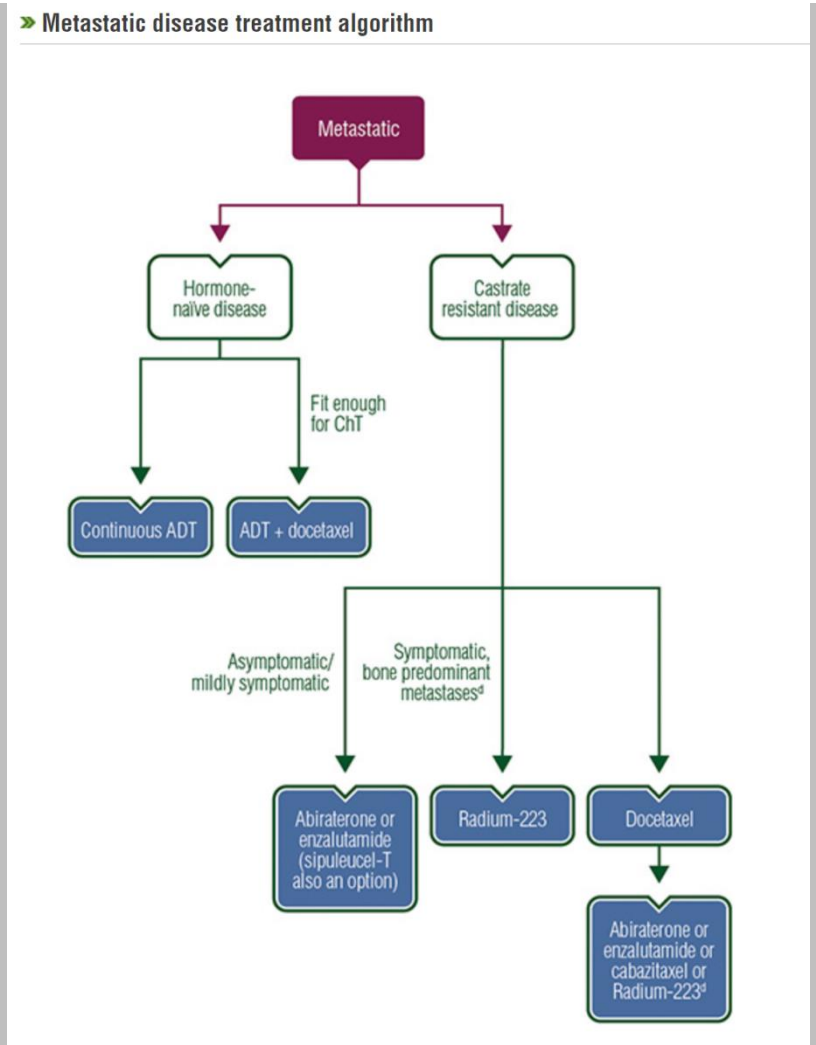
No. at Risk

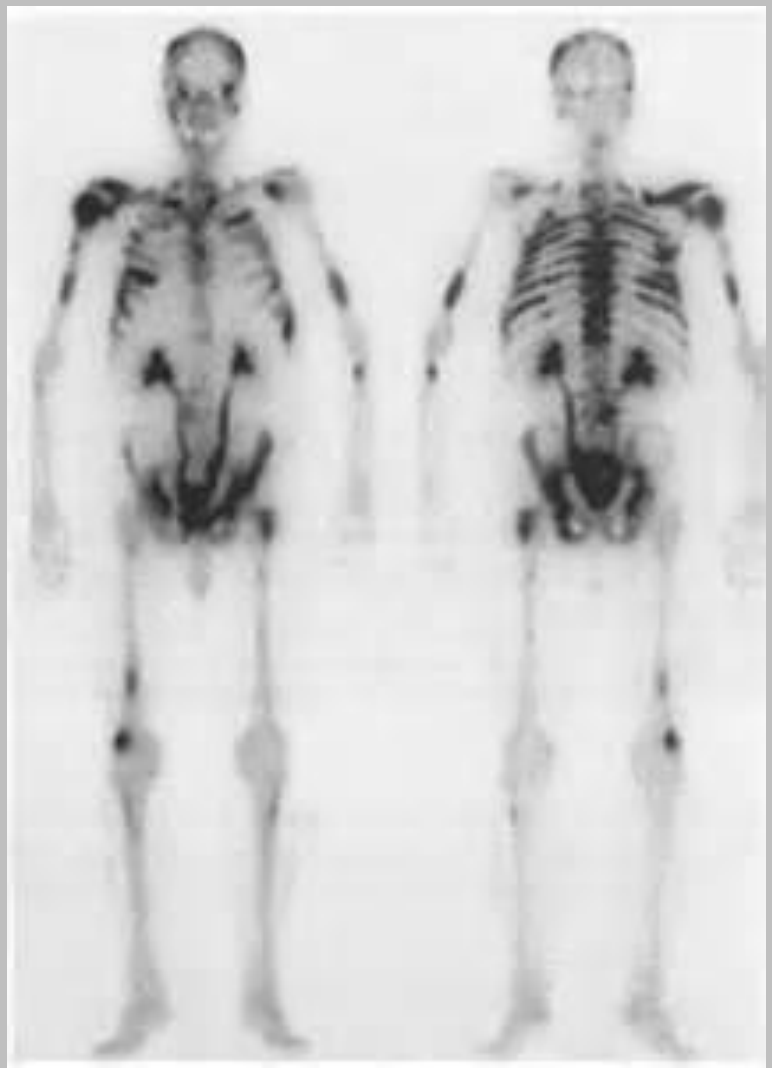
Radium-223	614	496	342	199	129	63	31	8	8	1	0
Placebo	307	211	117	56	36	20	9	7	4	1	0

Ra223-XOFIGO

THERAPEUTIC INDICATION: treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases.

ESMO 2016 Update – Prostate Cancer Algorithms



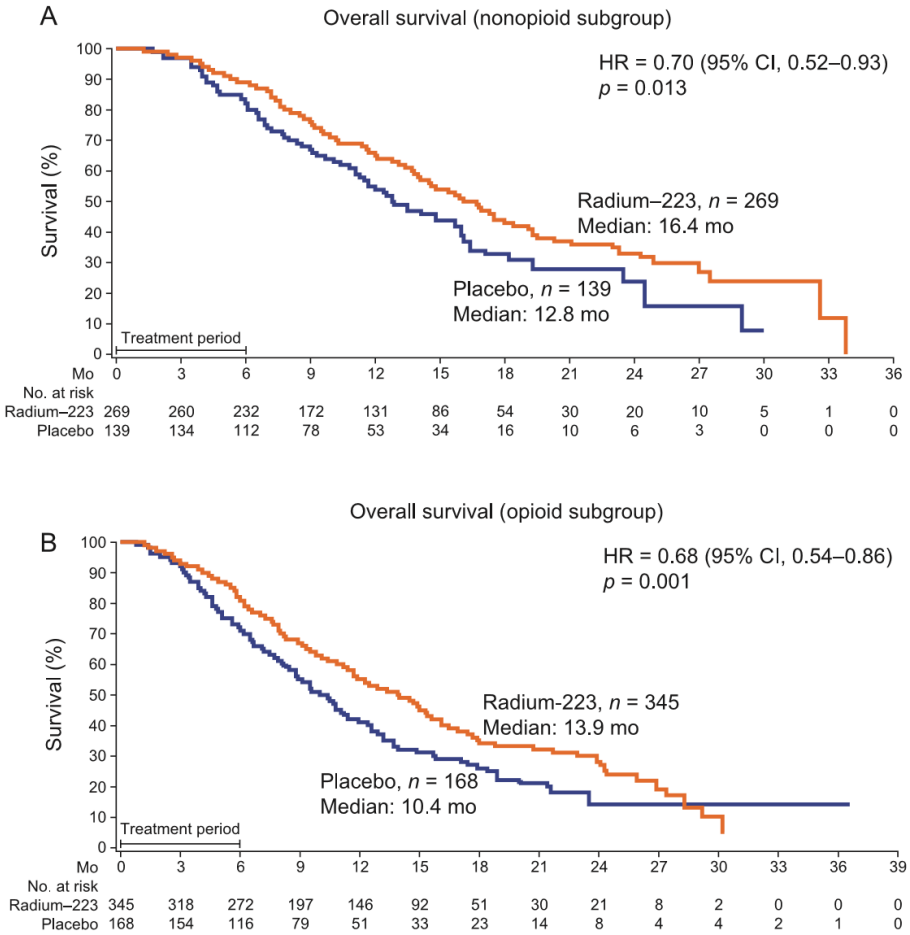


Efficacy and Safety of Radium-223 Dichloride in Symptomatic Castration-resistant Prostate Cancer Patients With or Without Baseline Opioid Use From the Phase 3 ALSYMPCA Trial

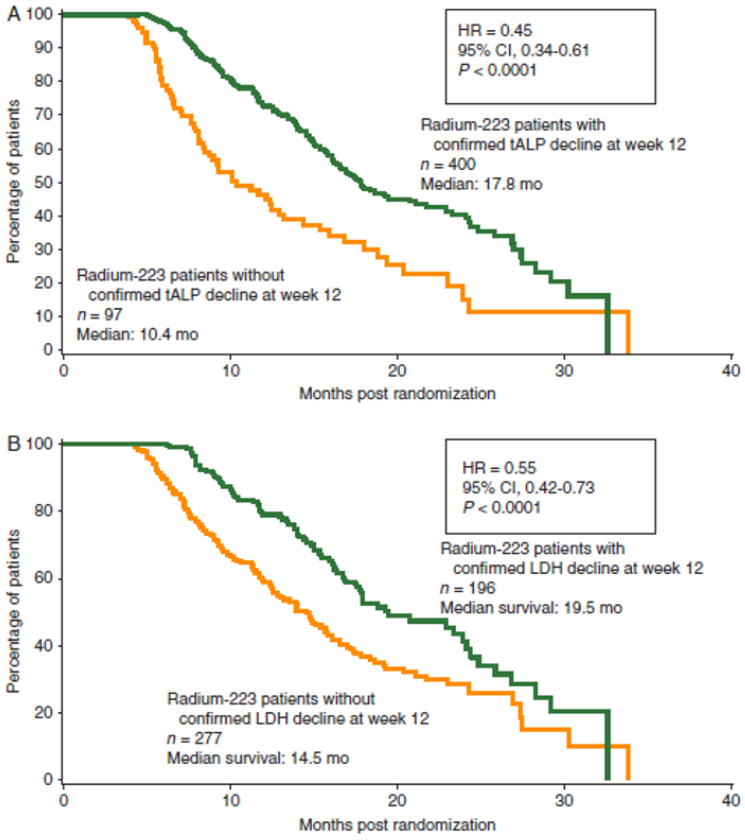
Christopher Parker[a,*], *Steven E. Finkelstein*[b], *Jeff M. Michalski*[c], *Joe M. O'Sullivan*[d], *Øyvind Bruland*[e], *Nicholas J. Vogelzang*[f], *Robert E. Coleman*[g], *Sten Nilsson*[h], *Oliver Sartor*[i], *Rui Li*[j], *Monica A. Seger*[j], *David Bottomley*[k]

[a] *Royal Marsden Hospital, Sutton, London, UK;* [b] *Cancer Treatment Centers of America, Tulsa, OK, USA;* [c] *Washington University School of Medicine, St Louis, MO, USA;* [d] *Center for Cancer Research and Cell Biology, Queen's University, Belfast, UK;* [e] *Norwegian Radium Hospital, Oslo, Norway;* [f] *Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA;* [g] *University of Sheffield, Sheffield, South Yorkshire, UK;* [h] *Karolinska University Hospital, Stockholm, Sweden;* [i] *Tulane Cancer Center, New Orleans, LA, USA;* [j] *Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA;* [k] *St. James University Hospital, Leeds, Yorkshire, UK*

Eur J Cancer. 2017



Análisis del valor pronóstico y predictivo de los biomarcadores a nivel basal y su evolución durante el tratamiento del estudio ALSYMPCA.



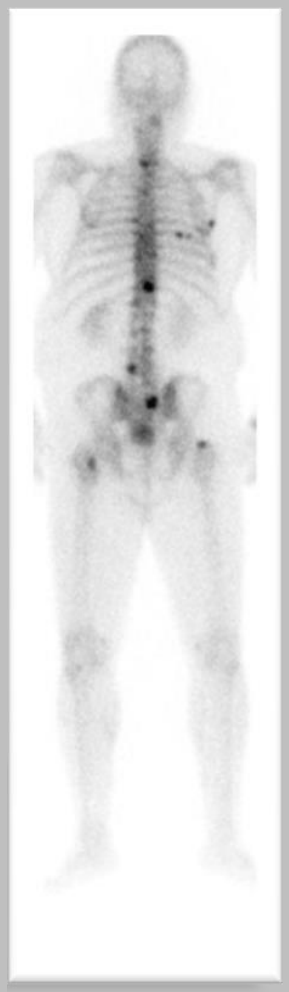
Los pacientes con una **disminución de la FA a la sem12 tienen una reducción del riesgo de muerte del 55%.**

La reducción de LDH a la sem12 contribuyo en mucha menor medida al efecto beneficioso de radio en la OS.

El análisis de PTE (proportional treatment effect) de los cambios de FA, LDH o PSA durante el tratamiento no mostró efecto subrogado sobre la supervivencia.

Sartor, Annals Oncology, 2017

Criteria prior RN treatment



•Life expectancy > 6 months

•Two or more skeletal metastases (≥2 hot spots) on bone scintigraphy

• Laboratory requirements:

a. Absolute neutrophil count (ANC) ≥ 1.5 x 109 /L b

b. Platelet count ≥100 x109 /L c.

c. Hemoglobin ≥9.0 g/dL (90 g/L; 5.6 mmol/L) without transfusion or erythropoietin support within 4 weeks prior to screening

d. Total bilirubin level ≤ 1.5

•Written, signed informed consent. Subject must be able to understand and be willing to sign the written informed consent form (ICF). A signed ICF must be appropriately obtained prior to the conduct of any study-specific procedure.

XOFIGO
Treatment methodology

First administration

Haematological evaluation of patients must be performed at baseline and prior to every dose of Xofigo.

Before the first administration, the absolute neutrophil count ANC ≥ 1.5 x 10^9/l

Platelet count ≥ 100 x 10^9/l

Haemoglobin ≥ 10.0 g/dl.

Before subsequent administrations

ANC ≥ 1.0 x 10^9/l

Platelet count ≥ 50 x 10^9/l.

In case there is no recovery in these values within 6 weeks after the last administration of Xofigo despite receiving standard of care, further treatment with Xofigo should only be continued after a careful benefit/risk evaluation

Ra-223
Staff protection

Dispensing and activity measurements

Fume cupboard

Dispense by unit volume

Dose-calibrator activity confirmation

Protective clothing

Gloves

Gown/apron

Overshoes

Mask/glasses

Syringe shield: plastic

Ra223

Calculation of activity measurements

EUROPE 12 noon Central European Time	
Day from reference date	**Physical decay factor**
-14	2.34
-13	2.20
-12	2.07
-11	1.95
-10	1.83
-9	1.73
-8	1.62
-7	1.53
-6	1.44
-5	1.35
-4	1.27
-3	1.20
-2	1.13
-1	1.06
0	1.00
1	0.94
2	0.89
3	0.83
4	0.78
5	0.74
6	0.69
7	0.65
8	0.62
9	0.58
10	0.55
11	0.51
12	0.48
13	0.45
14	0.43

- ✓ 50 kBq/kg weight
- ✓ Concentration 1000kBq/ml
- ✓ Decay correction

$$\text{Volume (mL)} = \frac{\text{Weigth (kg) x 50}}{\text{Decay factor x 1000kBq/ml}}$$

Ra223

ADMINISTRATION

Licensed RI operator nurse

Outpatient procedure

Well-ventilated room

Usual protective clothing

Secure, peripheral canula

Slow i.v. Injection over 1 minute

10-20 mL 0.9% saline flush

Injection site reactions

Grade 1 and 2 injection site reactions, such as erythema, pain and swelling, were reported in 1.2% of patients treated with Xofigo.

Ra223

Pautas de seguimiento
Seguridad de paciente

POST-TREATMENT ADVICE FOR PATIENTS

Predominant GI excretion: minor GI disturbance

Minimal urinary excretion: contamination risk low

Normal hygiene: contamination risk low

Family members/carers exposure:

Dose rate at 1 m = 0,05 uSv/h

No close contact restrictions

Patient card or repord to explain that they have been treated

With a radionuclide (in case of emergency surgery or security issues)

XOFIGO

Adverse reactions reported in clinical trials in patients treated with Xofigo

System Organ Class (MedDRA)	Very common	Common	Uncommon
Blood and lymphatic system disorders	Thrombocytopenia	Neutropenia, Pancytopenia, Leukopenia	Lymphopenia
Gastrointestinal disorders	Diarrhoea, Vomiting, Nausea		
General disorders and administration site conditions		Injection site reactions	

INFREQUENT PATIENT COMPLAINTS

Temporary increase in bone pain

Gastrointestinal disorders

Factores asociados a un riesgo superior de toxicidad hematológica

Original Study

Hematologic Safety of Radium-223 Dichloride: Baseline Prognostic Factors Associated With Myelosuppression in the ALSYMPCA Trial

Nicholas J. Vogelzang,[1] Robert E. Coleman,[2] Jeff M. Michalski,[3] Sten Nilsson,[4] Joe M. O'Sullivan,[5] Christopher Parker,[6] Anders Widmark,[7] Marcus Thuresson,[8] Lei Xu,[9] Joseph Germino,[10] Oliver Sartor[11]

Abstract

Radium-223 was minimally myelosuppressive. Multivariate analyses of data from ALSYMPCA patients identified baseline factors that may increase hematologic toxicity risk with radium-223. Extent of disease and degree of prostate-specific antigen elevation were predictive of grade 2-4 anemia; prior docetaxel, and decreased hemoglobin and platelets were predictive of grade 2-4 thrombocytopenia. Patients with these factors should be closely monitored during radium-223 therapy.

Background: Myelosuppression is common in patients with progressive castration-resistant prostate cancer and bone metastases. Radium-223 prolongs overall survival in these patients but may cause myelosuppression; understanding risk factors will improve clinical decision making. We describe hematologic safety of radium-223 in ALSYMPCA and post hoc analyses identifying patients at increased risk for hematologic toxicity. **Patients and Methods:** Hematologic parameters and adverse events were analyzed. Multivariate analyses assessing baseline risk factors for hematologic toxicities were performed separately for radium-223 and placebo patients. **Results:** Nine hundred one patients received radium-223 (n = 600) or placebo (n = 301); 65% of radium-223 and 48% of placebo patients had the full 6 cycles. Grade 3/4 thrombocytopenia was more common in radium-223 versus placebo patients (6% vs. 2%). Logistic regression analyses identified significant baseline predictors for grade 2-4 hematologic toxicities related to radium-223 treatment: extent of disease (6-20 vs. < 6 bone metastases; odds ratio [OR] = 2.76; $P = .022$) and elevated prostate-specific antigen (OR = 1.65; $P = .006$) for anemia; prior docetaxel (OR = 2.16; $P = .035$), decreased hemoglobin (OR = 1.35; $P = .008$), and decreased platelets (OR = 1.44; $P = .030$) for thrombocytopenia. Neutropenia events were too few in placebo patients for a comparative analysis. There were no significant associations between hematologic toxicities and number of radium-223 injections received (4-6 vs. 1-3). **Conclusion:** Radium-223 has a favorable safety profile with a low myelosuppression incidence. Understanding baseline factors associated with myelosuppression may assist clinicians in avoiding severe myelosuppression events with radium-223.

Vogelzang NJ, et al. Clin Genitourin Cancer. 2016. In Press.

Un subanálisis de la seguridad de dicloruro de ^{233}Ra identificó los factores basales asociados a un riesgo superior de toxicidad hematológica (grado 2-4).

Los **factores de riesgo para trombopenia G2-4** fueron docetaxel previo, y niveles reducidos de plaquetas y hemoglobina.

Los **factores de riesgo para anemia G2-4** fueron la extensión de la enfermedad (6-20 vs. < 6 metástasis) y elevado PSA .

GUIÓN

PRINCIPIOS DE LA TERAPIA CON RADIONÚCLIDOS

APLICACIONES CLÍNICAS DE LA TERAPIA CON RN ALFA

CARACTERÍSTICAS ESPECÍFICAS DE LA DOSIMETRÍA DE LOS RN

PERSPECTIVAS DE FUTURO DE LA TERAPIA CON RN ALFA

European Journal of Nuclear Medicine and Molecular Imaging (2018) 45:824–845
https://doi.org/10.1007/s00259-017-3900-4

GUIDELINES

EANM guideline for radionuclide therapy with radium-223 of metastatic castration-resistant prostate cancer

Thorsten D. Poeppel[1] · Daria Handkiewicz-Junak[2] · Michael Andreeff[3] · Alexander Becherer[4] · Andreas Bockisch[1] · Eva Fricke[5] · Lilli Geworski[6] · Alexander Heinzel[7] · Bernd J. Krause[8] · Thomas Krause[9] · Markus Mitterhauser[10,11] · Wilfried Sonnenschein[1] · Lisa Bodei[12] · Roberto C. Delgado-Bolton[13] · Michael Gabriel[14,15]

Table 5 Absorbed radiation doses for Xofigo®, considering its observed biodistribution and specific characteristics (according to the SmPC [2])

Target organ	Alpha emission* [Gy/MBq]	Beta emission [Gy/MBq]	Gamma emission [Gy/MBq]	Total dose [Gy/MBq]	Coefficient of variation# (%)
Adrenals	0	0.00002	0.00009	0.00012	56
Brain	0	0.00002	0.00008	0.0001	80
Breasts	0	0.00002	0.00003	0.00005	120
Gallbladder wall	0	0.00002	0.00021	0.00023	14
Lower large intestine wall	0	0.0456	0.00085	0.04645	83
Small large intestine wall	0.00319	0.0036	0.00047	0.00726	45
Stomach wall	0	0.00002	0.00012	0.00014	22
Upper large intestine wall	0	0.0315	0.00082	0.03232	50
Heart wall	0.00161	0.00007	0.00005	0.00173	42
Kidneys	0.00299	0.00011	0.00011	0.0032	36
Liver	0.00279	0.0001	0.00008	0.00298	36
Lungs	0	0.00002	0.00005	0.00007	90
Muscle	0	0.00002	0.0001	0.00012	41
Pancreas	0	0.00002	0.00009	0.00011	43
Red marrow	0.132	0.00642	0.0002	0.13879	41
Osteogenic cells	1.14	0.0149	0.0003	1.15206	41
Skin	0	0.00002	0.00005	0.00007	79
Spleen	0	0.00002	0.00007	0.00009	54
Testes	0	0.00002	0.00006	0.00008	59
Thymus	0	0.00002	0.00003	0.00006	109
Thyroid	0	0.00002	0.00005	0.00007	96
Urinary bladder wall	0.00371	0.00016	0.00016	0.00403	63
Whole body	0.0222	0.00081	0.00012	0.02311	16

SmPC: summary of product characteristics

* As there was no uptake of radium-223 in most of the soft tissues observed, the alpha contribution to the total organ dose was set to zero for these organs

Referring to the population in whom the biodistribution was assessed

Table 3. Estimated equivalent dose after i.v. injection of a dosage of 50 kBq/kg of ^{223}Ra

Target organs	Dose equivalents (Sv)
Adrenals	5.60×10^{-2}
Urinary bladder	5.70×10^{-2}
Brain	5.55×10^{-2}
Breast	5.55×10^{-2}
Gall bladder	5.60×10^{-2}
Heart wall	5.55×10^{-2}
Kidneys	5.60×10^{-2}
Liver	6.35×10^{-1}
Muscle	5.60×10^{-2}
Ovaries	5.65×10^{-2}
Pancreas	5.60×10^{-2}
Testes	5.55×10^{-2}
Thyroid	5.55×10^{-2}
Bone surface	13.05
Stomach	5.60×10^{-2}
Small intestine	5.65×10^{-2}
Upper large intestine	1.68×10^{-1}
Lower large intestine	3.67×10^{-1}
Skin	5.55×10^{-2}
Spleen	5.55×10^{-2}
Thymus	5.55×10^{-2}
Uterus	5.60×10^{-2}
Expiratory tract	5.55×10^{-2}
Lung	5.55×10^{-2}
Colon	2.54×10^{-1}
Thoracic lymph node	5.55×10^{-2}
Esophagus	5.55×10^{-2}
Gonads	5.65×10^{-2}
Remainder	5.60×10^{-2}

NOTE: The data represent ^{223}Ra in equilibrium with the daughter radionuclides and were calculated according to the ICRP-67 recycling model for radium. A quality factor of 5.0 for α particles was assumed.

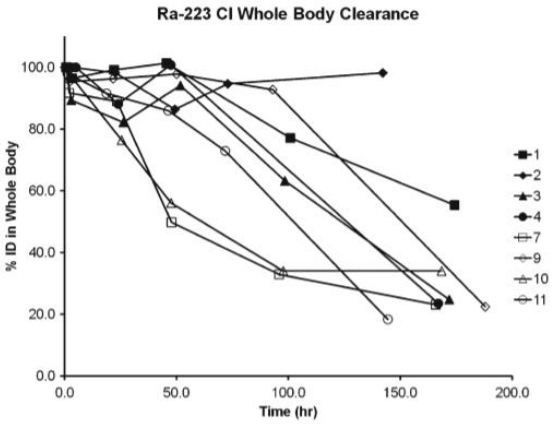


Fig. 1 Decay-corrected percentage of ^{223}Ra retained in the whole body (initial pre-void counts taken as 100 %) in patients (n=8) over a period of approximately 1 week post-administration

Table 4 Estimated urinary and fecal excretion based on whole-body decay-corrected measurements and imaging

Patient	Percent of injected activity (%ID) excreted in urine, first void	Fraction (%ID) in large intestine at ~24 h (time of whole-body scan)	Whole-body excretion	
			Time (days)	Total percent excreted (%ID)
1	4	43	7.3	45
2	–	61	5.9	2
3	11	43	7.2	75
4	–	52	7.0	76
6	–	49	–	–
7	8	58	6.9	77
9	5	59	7.8	78
10	2	40	7.0	66
11	2	53	6.0	82
Median	5	52	7.0	76
Mean±standard deviation	5 %±3	51 %±8	6.9±0.6	63 %±27

Phase I study to better profile the pharmacokinetics, pharmacodynamics, and biodistribution of this agent.
Ten patients received either 50, 100, or 200 kBq of 223Ra per kilogram of body weight.
Six of these ten patients received a second dose of 50 kBq/kg.
Kinetics and biodistribution were assessed by serial blood sampling, planar imaging, and whole-body counting.
Pharmacodynamic assessment was based on measurements of prostate-specific antigen, bone alkaline phosphatase, and serum N-telopeptide.
Safety was also assessed.

Pharmacokinetic studies showed rapid clearance of 223Ra from the vasculature, with a median of 14 % (range 9– 34 %), 2 % (range 1.6–3.9 %), and 0.5 % (range 0.4–1.0 %) remaining in plasma at the end of infusion, after 4 h, and after 24 h, respectively.

Biodistribution studies showed early passage into the small bowel and subsequent fecal excretion with a median of 52 % of administered 223Ra in the bowel at 24 h.

Urinary excretion was relatively minor (median of 4 % of administered 223Ra).
Bone retention was prolonged.
No dose limiting toxicity was observed.
Pharmacodynamic effects were observed (alkaline phosphatase and serum N-telopeptides) in a significant fraction of patients

ES NECESARIA LA DOSIMETRÍA PERSONALIZADA?

Conocer la dosis administrada a la lesión diana

- Efecto terapéutico
- Monitorización terapéutica
- Decisión de opciones terapéuticas

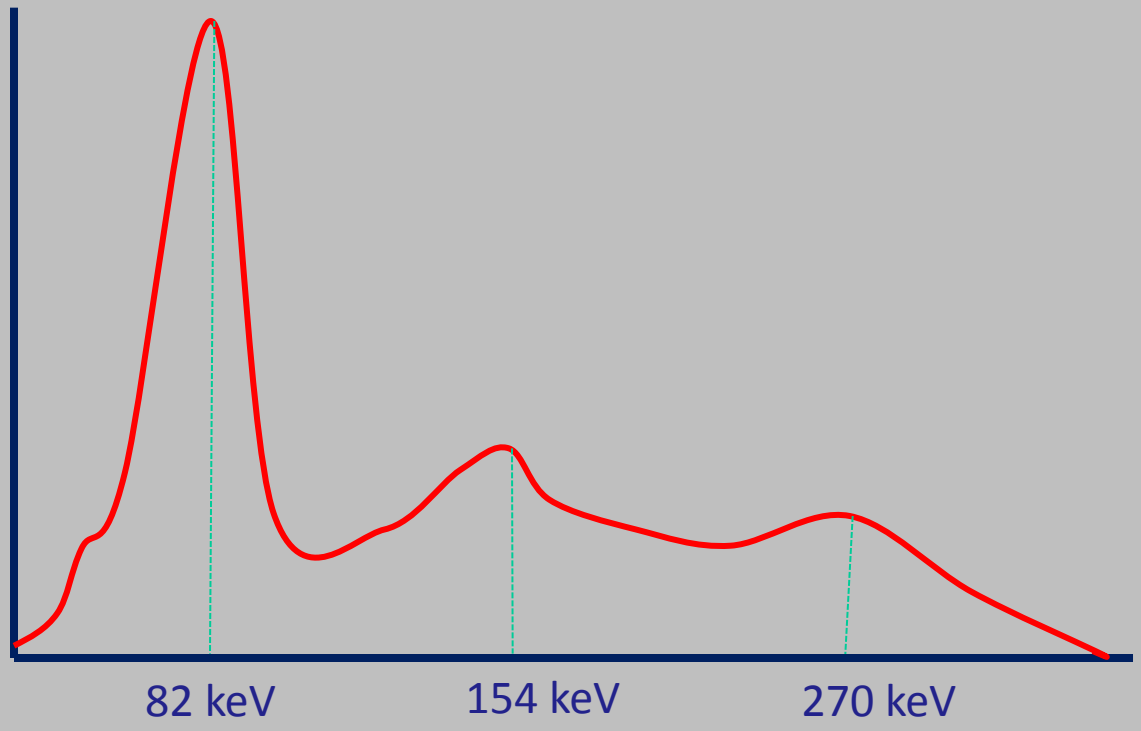
Conocer la dosis administrada a órganos no diana

REQUERIMIENTOS:

- ✓Perfil de la expresión biológica tumoral
- ✓Biodistribución y farmacocinética
- ✓Farmacodinámica
- ✓Modificación según la respuesta al tto.
- ✓Evolución del fenotipo tumoral

Ra223 Imaging

Quantitative imaging of 223Ra-chloride for targeted alpha-emitting radionuclide therapy of bone metastases.

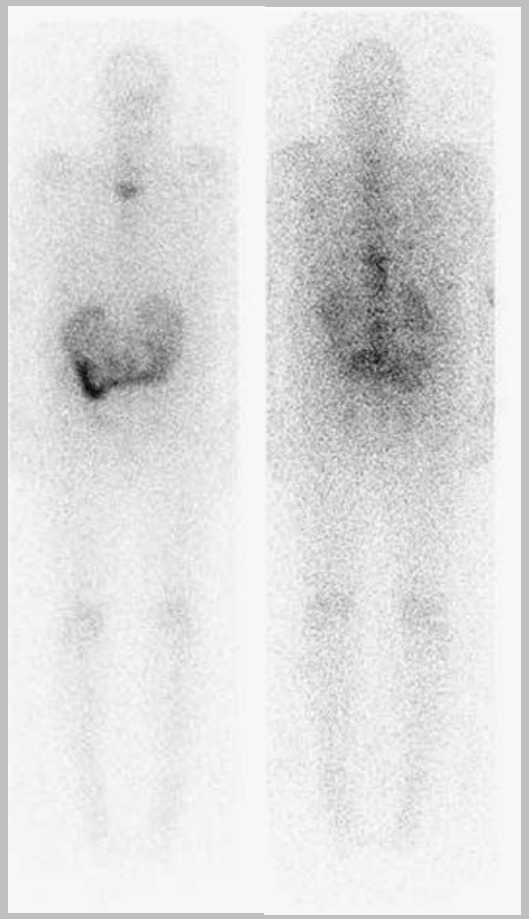


Hindorf C. Nucl Med Commun 2012.

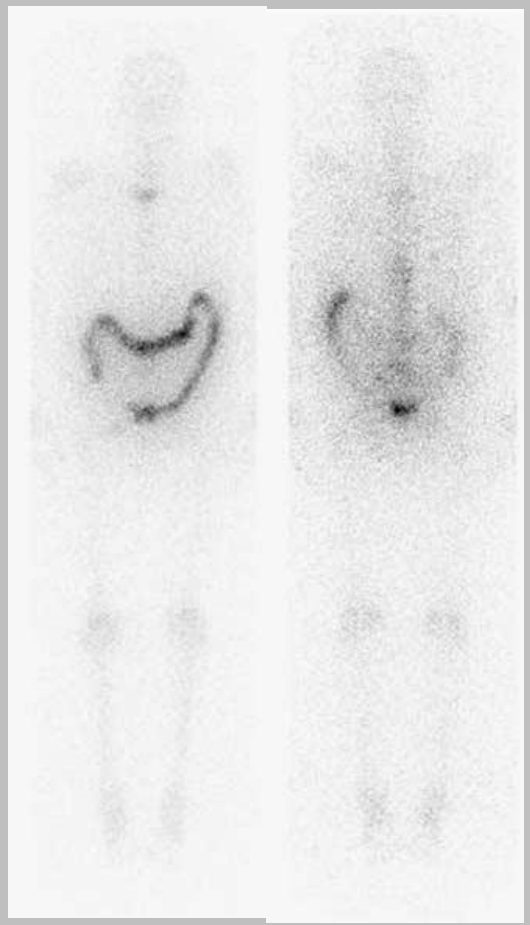
Ra-223

Biodistribution y fármacocinética

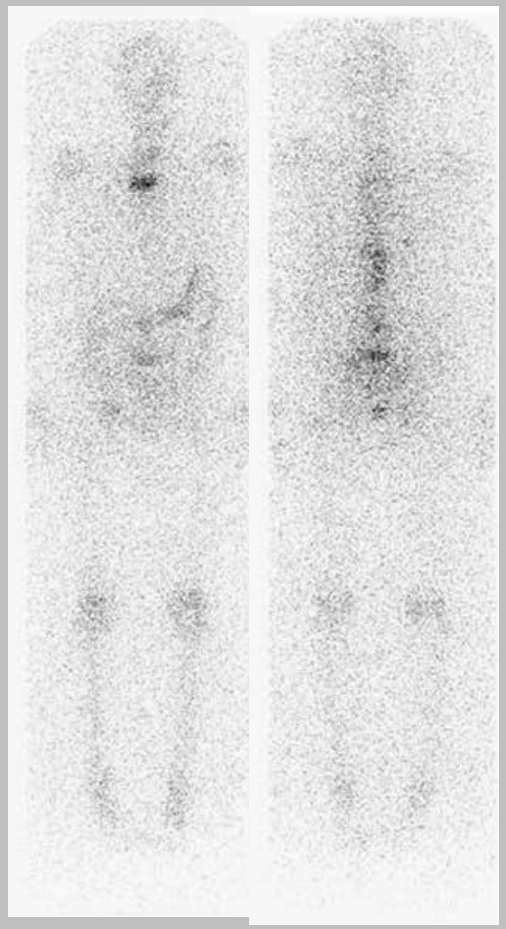
Se requiere el seguimiento por imágenes de la retención del radiofármaco en las lesiones para establecer el tiempo de exposición a la radiación de los tejidos



4 hours



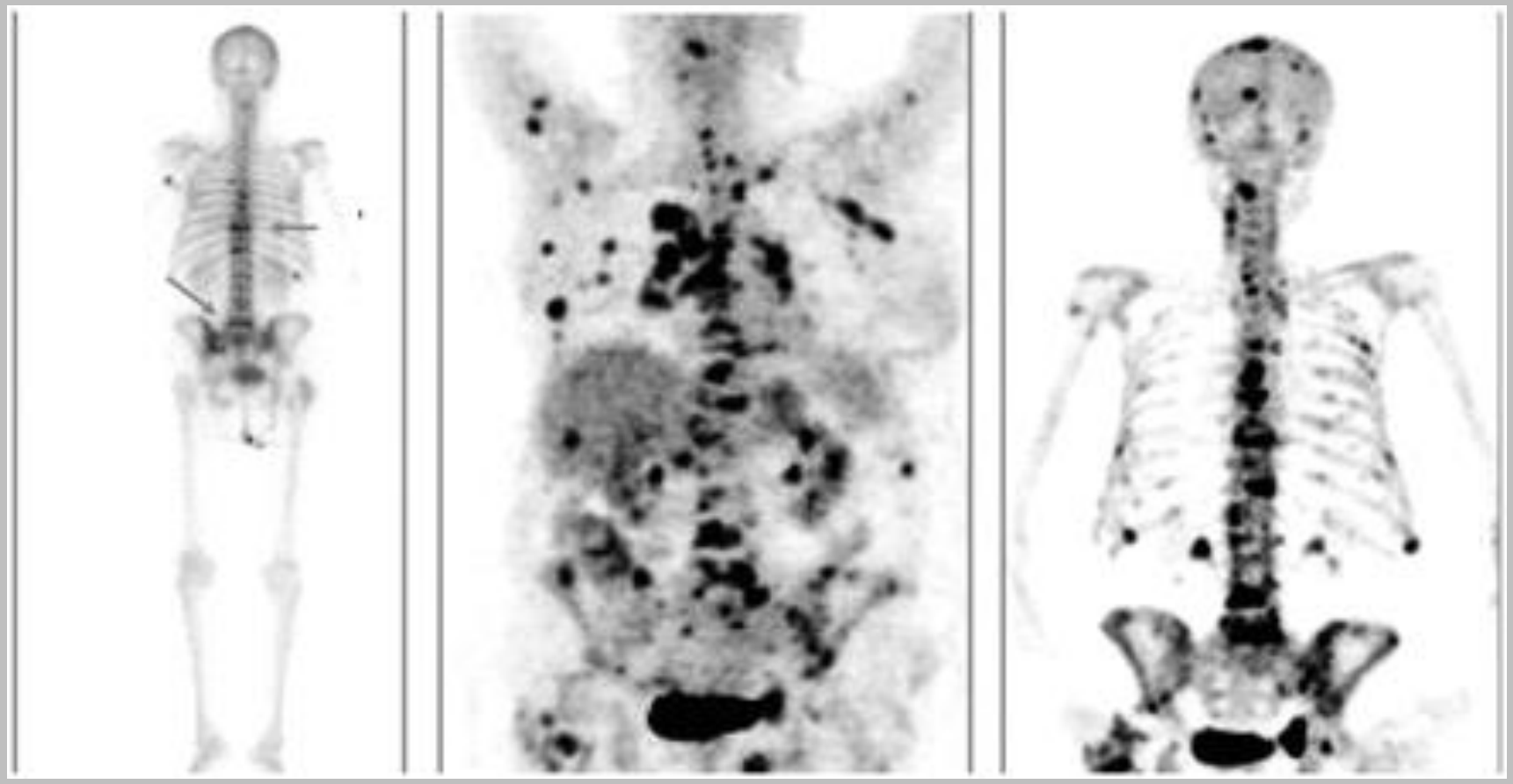
48 hours



144 hours

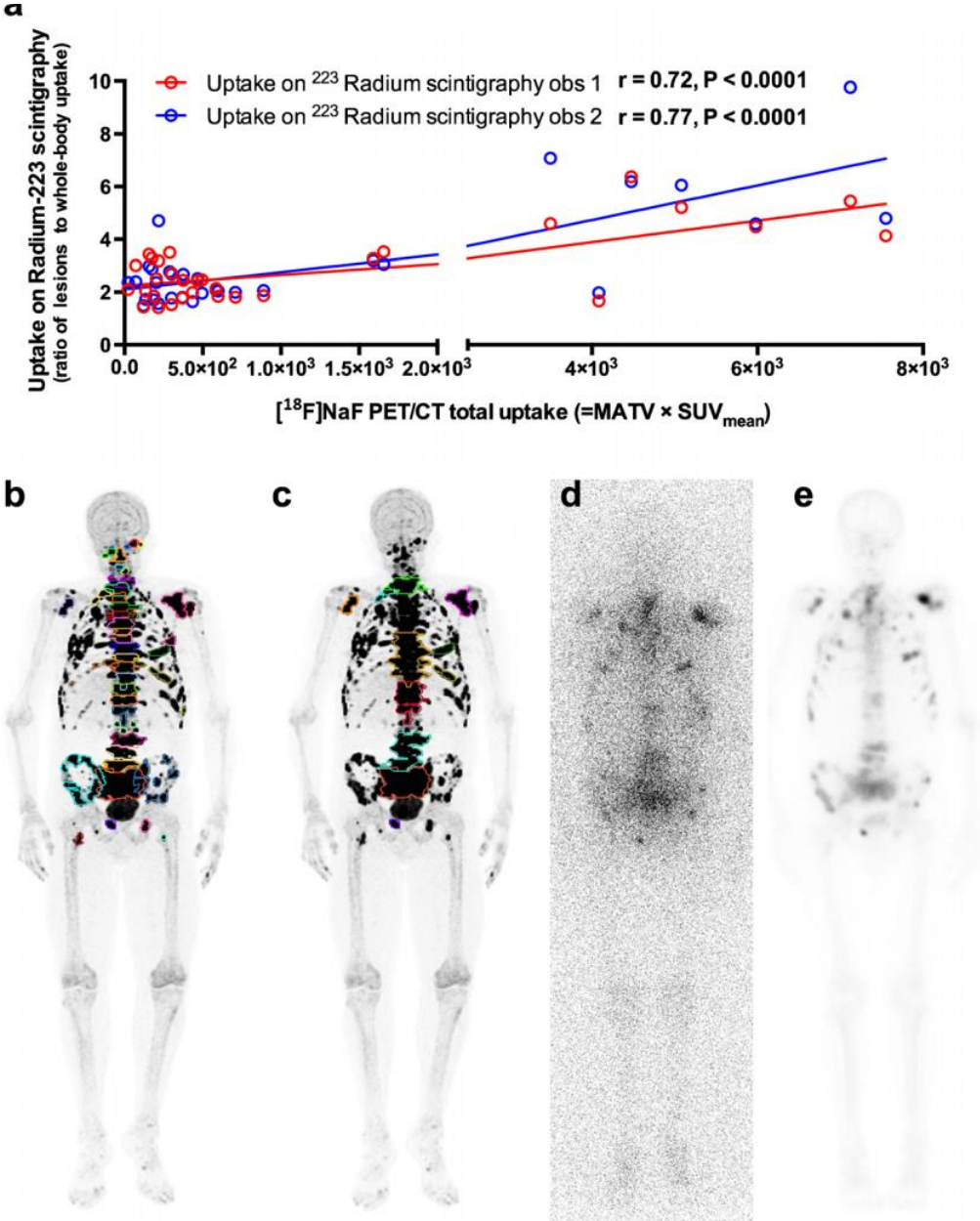
Hindorf C. Nucl Med Commun 2012.

Valoración de la carga tumoral en función de la diana y el radiofármaco utilizado.
Relación con la selección de opción terapéutica y estimación de la dosimetría



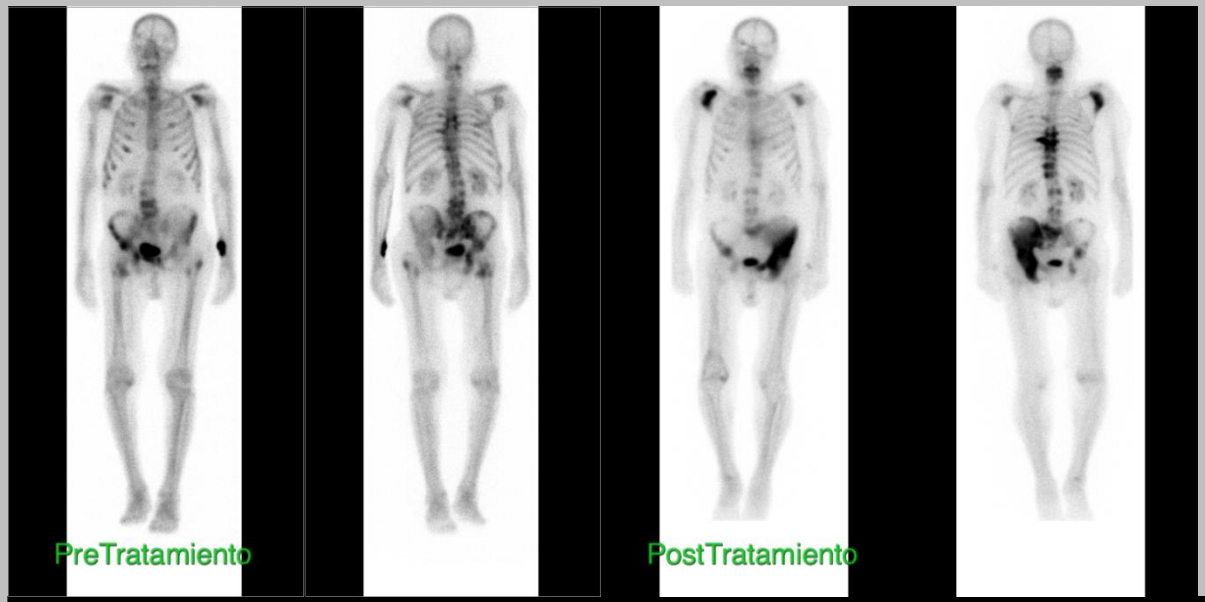
^{99m}Tc-MDP ^{18}F-FDG ^{18}FNa

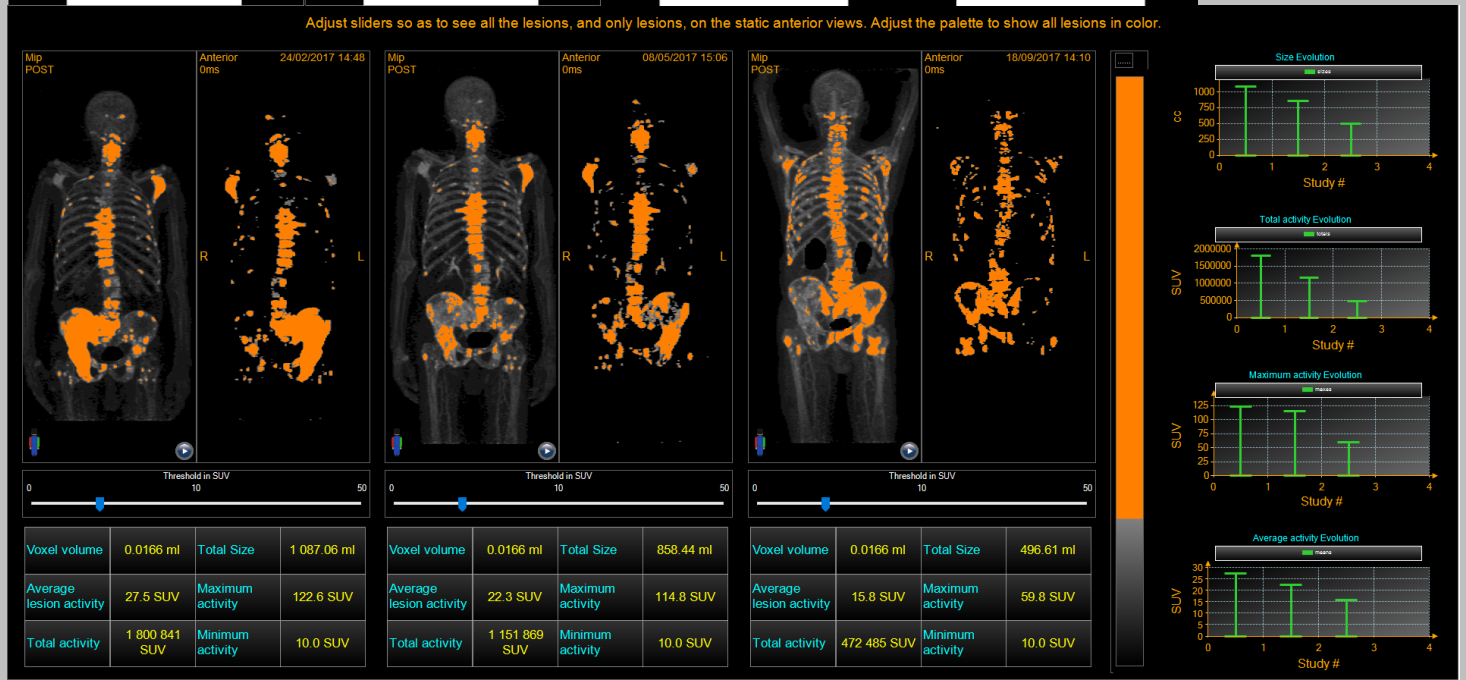
Correlation between total [18F]NaF uptake in metastases and relative radium-223 uptake on biodistribution scintigraphy. (surrogate biomarkers)



Letellier A, Mol Imaging Biol 2017

Modificación de la biodistribución de los radiofármacos según la respuesta al tto





A Phase 1, Open-Label Study of the Biodistribution, Pharmacokinetics, and Dosimetry of ^{223}Ra-Dichloride in Patients with Hormone-Refractory Prostate Cancer and Skeletal Metastases

J Nucl Med 2015

Sarah J. Chittenden[1], Cecilia Hindorf[2], Christopher C. Parker[3], Valerie J. Lewington[4], Brenda E. Pratt[1], Bernadette Johnson[3], and Glenn D. Flux[1]

[1]Joint Department of Physics, Royal Marsden Hospital and Institute of Cancer Research, Sutton, Surrey, United Kingdom; [2]Department of Radiation Physics, Radionuklidcentralen, Skåne University Hospital Lund, Lund, Sweden; [3]Department of Urology, Royal Marsden Hospital, Sutton, Surrey, United Kingdom; and [4]Department of Nuclear Medicine, Guy's Hospital, London, United Kingdom

Six patients received 2 intravenous injections of 223Radichloride, 6 wk apart, at 100 kBq/kg of whole-body weight

The biodistribution, pharmacokinetics, and absorbed doses were determined from:

Activity retention measurements in the whole body
- After injection, before first void
- 1 h and thereafter every 2 h during the first day
- At least twice daily until discharge
- 96 and 144 h after injection

Individual organs
- insufficient counting rate to acquire SPECT data
- WB PLANAR IMAGING: The first scan 0–4 h after injection
- Subsequent scans were acquired at 24, 48, 96, and 144 h after injection.

Blood
- Samples were taken before injection; immediately after injection; then at 15, 30, and 45 min and 1, 2, 4, 24, 48, 96, and 144 h after injection.

Urine
- time periods 0–4, 4–8, 8–24, and 24–48 h after injection

Feces
- All feces excreted by each patient from injection to approximately 48 h were collected

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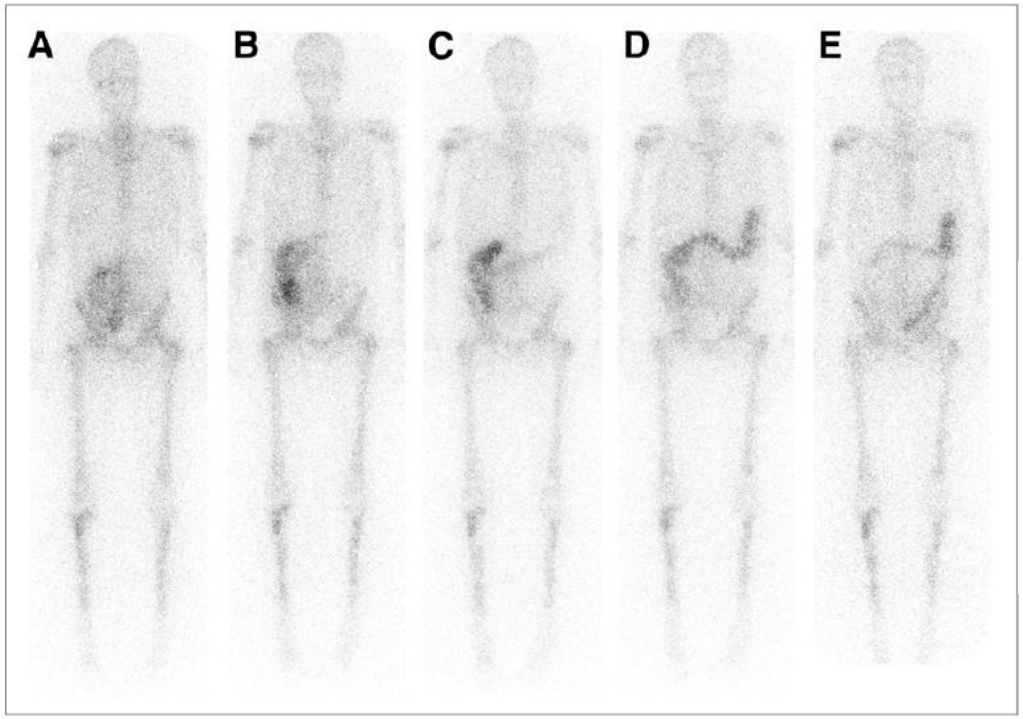

FIGURE 1. Whole-body anterior images for patient 3 acquired at 4 (A), 24 (B), 48 (C), 72 (D), and 144 h (E) after administration.

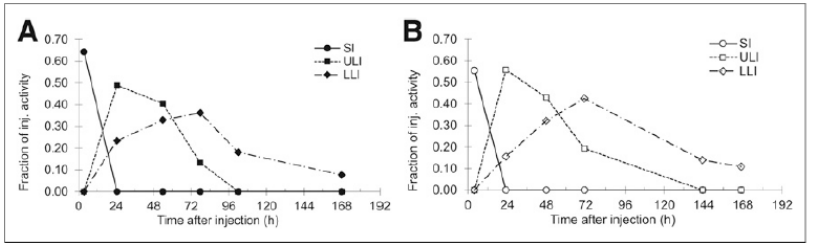

FIGURE 2. Activity retention curves in SI, ULI, and LLI for patient 1 for administration 1 (A) and administration 2 (B). inj = injected.

A Phase 1, Open-Label Study of the Biodistribution, Pharmacokinetics, and Dosimetry of ^{223}Ra-Dichloride in Patients with Hormone-Refractory Prostate Cancer and Skeletal Metastases

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Dosimetry

Regions of interest were delineated on the images over bone uptake with reference to the 99mTc-methylene diphosphonate bone scans acquired at pretreatment assessment. Activity in bone was calculated as the mean of the activity per unit mass in the right and left legs and skull, to avoid difficulties in interpretation due to gut and lesion uptake in the torso.

The activity in bone was assumed to be distributed on the cortical and trabecular bone surfaces, in a ratio relative to the total bone surface (38% on cortical bone surfaces and 62% on trabecular bone)

The cumulated activity in the gut was derived from regions of interest drawn over the areas of gut uptake on the whole-body scans.

In keeping with ICRP 100, the contribution of the a emission to the gut wall from the contents was taken to be 0

For imaged organs, cumulated activities were calculated by trapezoidal integration. The activity at time zero was assumed to equal the activity at the first image. The effective half-life as determined from the last 2 g-camera images was used for extrapolation from the last measurement to infinity.

The absorbed doses delivered to normal organs were calculated with Olinda/EXM with an a quality-weighting factor of 1.

Patient-specific mass corrections were made to the Olinda S values for the whole body but not for other organs because of insufficient anatomic information for accurate mass determination.

The total absorbed dose to the target region was calculated as the sum of the contributions from all source regions and included contributions from the decay of the daughter products of 223Ra.

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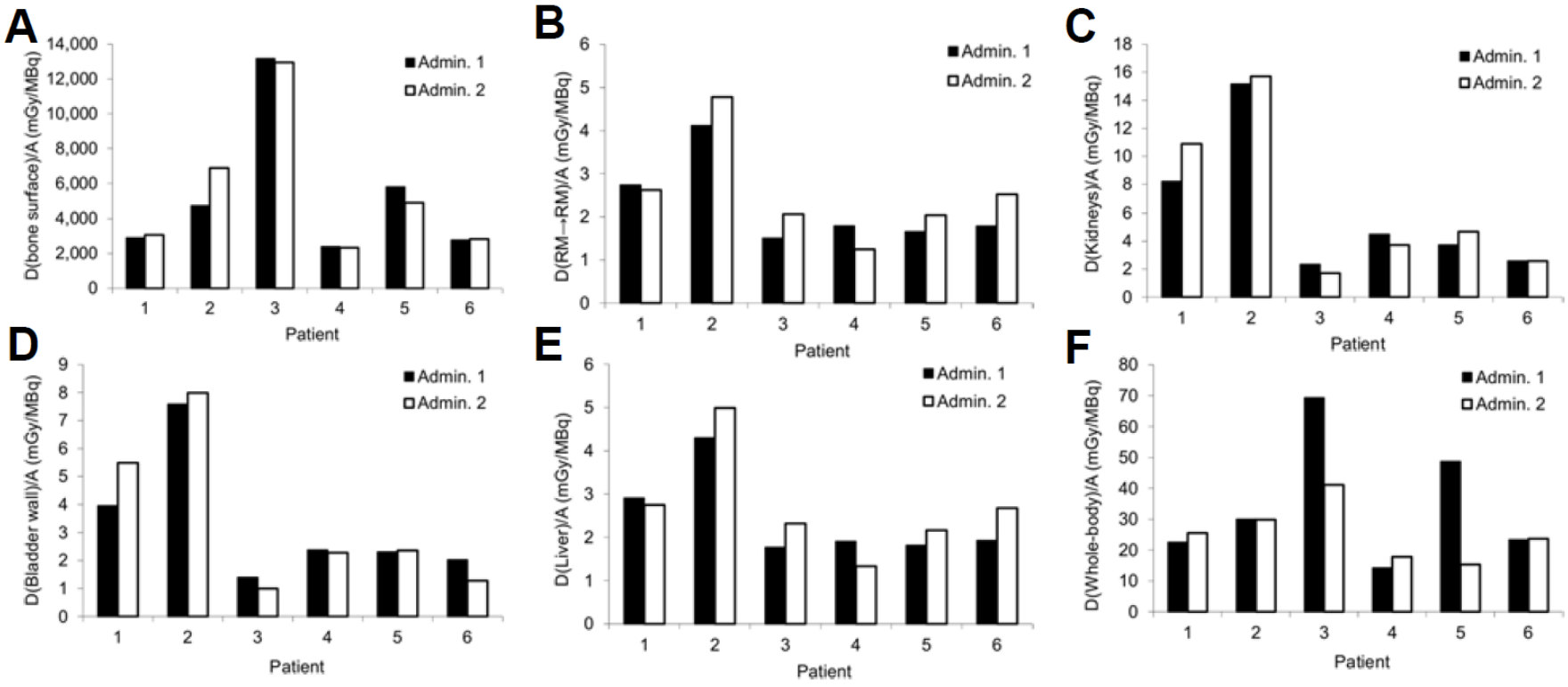

Figure 3: Absorbed dose (in mGy/ MBq) for A) Bone surfaces, B) Red marrow from blood, C) Kidneys, D) Bladder Wall, E) Liver, F) Whole-body.

A Phase 1, Open-Label Study of the Biodistribution, Pharmacokinetics, and Dosimetry of ^{223}Ra-Dichloride in Patients with Hormone-Refractory Prostate Cancer and Skeletal Metastases

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TABLE 2

Mean Residence Times and Absorbed Doses Delivered from Both Administrations

Organ	Mean residence time (h)	α absorbed dose (mGy/MBq)		β + γ absorbed dose (mGy/MBq)	
		Mean	Range	Mean	Range
SI wall	6.8	0	NA	5	3–10
ULI wall	29.2	0	NA	38	6–68
LLI wall	29.2	0	NA	61	5–176
Kidneys	0.1	6	2–15	<1	—
Red marrow, from blood	0.2	2	1–5	<1	—
Red marrow, from bone surfaces	—	408	177–994	9	4–22
Bone surfaces	97.0	5,378	2,331–13,118	21	9–51
Liver	0.3	2	1–5	<1	—
Urinary bladder wall	0.1	3	1–8	<1	—
Total body	154.8	29	14–66	1	1–3

NA = not applicable.

Eur J Nucl Med Mol Imaging (2016) 43:21–33
DOI 10.1007/s00259-015-3150-2

ORIGINAL ARTICLE

Dosimetry of bone metastases in targeted radionuclide therapy with alpha-emitting ^{223}Ra-dichloride

Massimiliano Pacilio[1] · Guido Ventroni[2] · Giuseppe De Vincentis[3] · Bartolomeo Cassano[4] · Rosanna Pellegrini[5] · Elisabetta Di Castro[3] · Viviana Frantellizzi[3] · Giulia Anna Follacchio[3] · Tatiana Garkavaya[3] · Leda Lorenzon[4] · Pasquale Ialongo[6] · Roberto Pani[5] · Lucio Mango[2]

9 pts

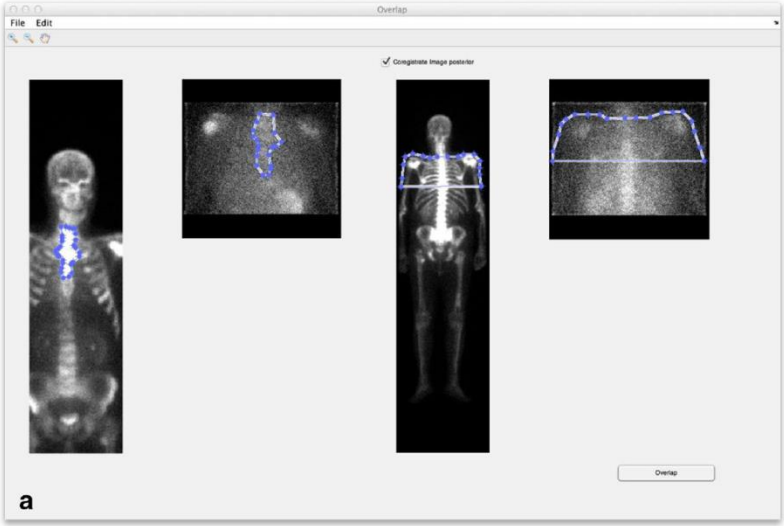
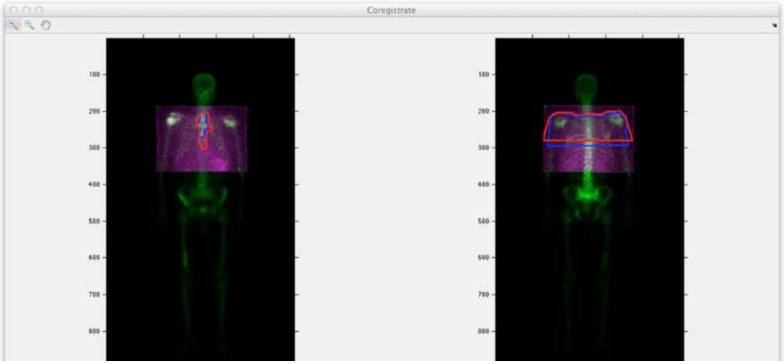


Fig. 1 Coregistration of the ^{99m}Tc-MDP WB images and the static ^{223}Ra images (acquired at 1.5 h after administration, patient 1) using the MATLAB toolkit (*left* anterior images, *right* posterior images): **a** loading the images and delineating the areas of interest, **b** coregistering the images



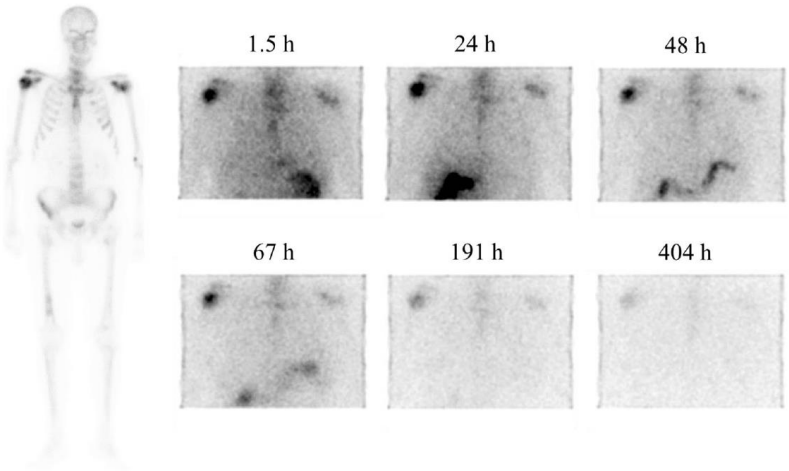


Fig. 2 ^{99m}Tc-MDP WB image and the series of anterior static images obtained at different times after administration of ^{223}Ra-dichloride in patient 1. The static images were acquired at 1.5, 24, 48, 67, 191 and 404 h

REVIEW ARTICLE

Imaging and dosimetry for radium-223: the potential for personalized treatment

GLENN D FLUX, PhD

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Br J Radiol 2017

Table 2. The mean absorbed doses delivered to the bone surface and red marrow from commonly used radionuclides for typical administrations

Target Volume	Total absorbed dose (Gy)				
	$^{89}Sr^{a}$	$^{153}Sm^{b}$	$^{186}Re^{c}$	^{223}Ra (ICRP)^{d}	^{223}Ra (measured)^{e}
Bone surface	2.6	17.6	1.8	17.3	54–303
Red marrow	1.7	3.9	1.7	1.7	4–23

^{223}Ra, radium-223; ^{186}Re, rhenium-186; ^{153}Sm, samarium-153; ^{89}Sr, strontium-89.
Values are based on administration levels in Lassmann and Nosske,[28] Chittenden et al[32] and Bodei et al.[70]
[a]Fixed activity of 150 MBq.
[b]Administered activity of 37 MBq kg^{-1}, based on a 70-kg male.
[c]Administered activity 1295 MBq.
[d]Six administrations of 55 kBq kg^{-1}, based on a 70-kg male.
[e]Six administrations of 55 kBq kg^{-1}, based on a 70-kg male.

There is now a pressing need for larger multicentre trials to investigate the dosimetry and to optimize treatment regimens.

There is as yet little evidence for the absorbed doses delivered to metastatic deposits throughout the full course of six administrations or that the absorbed doses delivered to organs at risk over six administrations remain the same as those measured from one or two administrations

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DOI 10.1007/s00259-017-3707-3

EDITORIAL

The conflict between treatment optimization and registration of radiopharmaceuticals with fixed activity posology in oncological nuclear medicine therapy

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Formalization of the optimization principle in the new European Council Directive 2013/59

The new European Council Directive 2013/59 (http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32013L0059&from=EN), to be translated into national legislations before 6 February 2018, in article 56 (Optimisation) states: "*For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned and their delivery appropriately verified, taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure*". No doubt this statement holds for nuclear medicine therapy, since in article 4 of the same, directive definition 81 states that "*radiotherapeutic*" *means pertaining to radiotherapy, including nuclear medicine for therapeutic purposes*. The directive thus asks for dosimetry, as is routinely implemented in radiotherapy, using external beam or brachytherapy sources. However, in nuclear medicine therapy, absorbed dose planning is rarely performed. One of the main reasons is the amount of work needed for internal dosimetry that includes multiple whole-body counts or scintigraphy and sometimes blood samples over some days after administration.

The "intended purpose" in all therapeutic exposures is treatment efficacy against malignant disease. The optimization principle (as low as reasonably achievable, ALARA) of article 56, when applied in a therapy situation, states that absorbed doses to nontarget tissues should be kept reasonably low, but not so low as to lose efficacy. We think that this applies above all to the fight against life-threatening cancer. As a consequence, we believe that to adhere to the optimization principle in oncological patients, nuclear medicine therapy should be based on individualized dosimetry.

The maximum tolerable absorbed dose approach in nuclear medicine therapy

In contrast to external beam radiotherapy, in nuclear medicine therapy we have patients or situations where the absorbed dose to

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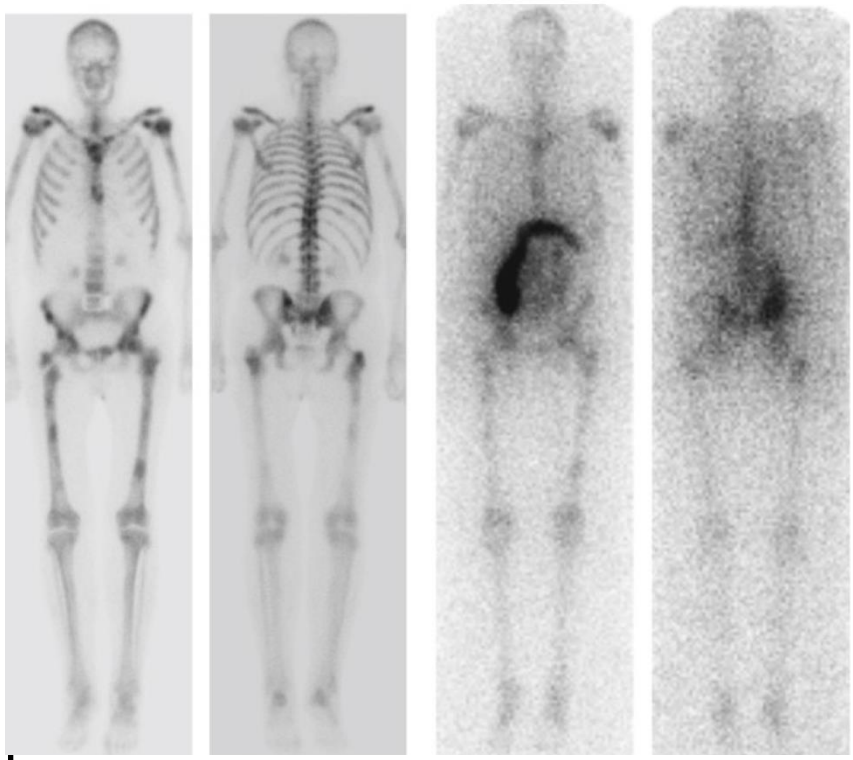
When regulatory agencies accept posology based only on fixed administrations, for instance as fixed activities and a fixed number of cycles (^{177}Lu DOTATATE), or a fixed activity per body mass (^{223}Ra), in order to comply with the package insert, therapists may be prevented from basing their prescriptions on the individual patient absorbed dose. As a consequence, the application of the optimization principle (article 56) of radiotherapy is prevented. In other words, package inserts containing only nondosimetric posology force therapists into conflict with article 56.

We consider that the responsibility for this lies with the registration and health authorities, who should be well aware of the above arguments before licensing a nondosimetric posology, excluding the possibility of dosimetry-based optimization.

In the present situation, where internal dosimetry is still not fully applied, *we propose that the package insert of any radioactive agent for therapy should indicate*, in parallel with conventional posology, *a dosimetry-based administration undertaken under the full responsibility of the therapy team*. Otherwise the optimization requirement will not be met for nuclear medicine therapy. A complete quality assurance programme should be in place to ensure accurate delivery of any prescribed treatment.



Eur J Nucl Med Mol Imaging
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LETTER TO THE EDITOR

Dosimetry in clinical radionuclide therapy: the devil is in the detail

Francesco Giammarile[1,2] · Kristoff Muylle[1,3] · Roberto Delgado Bolton[1,4] · Jolanta Kunikowska[1,5] · Uwe Haberkorn[6,7,8] · Wim Oyen[1,9]

In estimating the local absorbed dose, integral activities rely on accurate detection of the activity distribution over time

Due to the limited spatial resolution of imaging devices, calculations are based on approximations and it is important to note that it is not possible to perform the "perfect" dosimetry study.

To date, the need for and added value of dosimetry to optimize the therapeutic activity dose in the individual patient has been far from self-evident.

RNT dosimetry has not gained wide acceptance as a clinical tool in the nuclear medicine community because of the lack of accuracy and the complexity of time-consuming and costly procedures that potentially impose a significant burden on patients and healthcare systems.

The necessary specialized knowledge and experience required to perform accurate dosimetry studies are not available in all clinical centres, potentially limiting the offer to patients.

A number of clinical studies have completely omitted dosimetry, instead using fixed activities in all patients or individualized activity doses based on body weight or body surface area. Indeed, after seven decades of treating thyroid cancer patients, international guidelines still do not provide an unequivocal recommendation on the amount of radioiodine that should be given.

For these reasons, rather than seeking similarities to EBRT, it is more appropriate to develop RNT in a similar manner to chemotherapeutics, where dose calculation based on body weight or body surface area is common practice, independent of the tumour load and metastases.

The maximum tolerated dose of chemotherapeutics is established during clinical studies.

In subsequent clinical practice, the level of chemotherapeutic in blood is not checked to investigate the biodistribution and delivery to the tumours.

Official guidelines and recommendations for RNT do not include advanced dosimetric calculations. As in chemotherapy, fixed radioactivity doses (with or without visual assessment of pretherapy scans) or activity doses based on body weight or body surface area are considered sufficient in clinical practice for the main clinical RNT protocols

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LETTER TO THE EDITOR

Dosimetry in clinical radionuclide therapy: the devil is in the detail

Francesco Giammarile[1,2] · Kristoff Muylle[1,3] · Roberto Delgado Bolton[1,4] · Jolanta Kunikowska[1,5] · Uwe Haberkorn[6,7,8] · Wim Oyen[1,9]

Nevertheless, the European Council Directive 2013/59), to be translated into national legislations before 6 February 2018, stipulates that in medical exposures for radiotherapeutic purposes, including RNT, exposures of target volumes shall be individually planned and their delivery appropriately verified.

…Another important factor is represented by radiobiological effects of RNT at the cellular and molecular levels. Extrapolations made from EBRT are wrong, due to the fundamental differences in dose rate and the mechanisms of DNA damage. In RNT, with its decreasing dose rate, tumour DNA is repaired simultaneously with sublethal damage.
Furthermore, it has recently been reported that sensitivity to low absorbed dose, low dose rate radiation displays a genetically induced individual variability

In conclusion, although dosimetry is an undisputed aspect of radiopharmaceutical development, its clinical use to tailor the administered activity to an individual patient's needs is less evident. Data in the literature clearly and unequivocally establishing the potential of dosimetry to avoid underdosing and overdosing, and to standardize RNT methods are very scarce.
Furthermore, dosimetry is a difficult procedure that is not available everywhere as specialized knowledge and experience are required.
Thus, we must be cautious before transferring complex dosimetry to routine clinical practice, while robust scientific justification remains to be established.
First and foremost, the nuclear medicine community at large has the obligation to prove in prospective and randomized trials with adequate methodology, that complex dosimetry-based RNT has clinically relevant additional benefits for our patients over the currently used, well-established and very safe empirical dosing methods, whether using fixed-activity concepts or simple characteristics such as body weight and body surface area.

CONSIDERACIONES GENERALES A LA DOSIFICACIÓN PARA EL USO CLÍNICO DE LOS RADIOFÁRMACOS TERAPÉUTICOS

Los radiofármacos siguen la regulación de las agencias de medicamentos
Las aprobaciones siguen los resultados demostrados en ensayos clínicos
Estos se basan en criterios análogos a los utilizados para la aprobación de medicamentos convencionales
La eficacia y protección del paciente se define en los ensayos de seguridad Fase I-II
El escalado de dosis está determinado por la eficacia y efectos adversos
Las dosis son fijas y se han determinado en función de los estudios de seguridad
No está permitido el cambio de la administración de dosis fuera de las indicaciones de la ficha técnica

COMENTARIOS

La necesidad de saber si se ha tratado adecuadamente cada lesión se puede resolver mediante imágenes post terapéuticas del propio RF o usando RF diagnósticos subrogados (teranóstico)

Queda por demostrar si la dosimetría personalizada supera en eficacia terapéutica a los regímenes de dosis determinadas en los EC o permite mejorar la selección y personalización de la terapia de forma más eficiente que la actual

GUIÓN

PRINCIPIOS DE LA TERAPIA CON RADIONÚCLIDOS

APLICACIONES CLÍNICAS DE LA TERAPIA CON RN ALFA

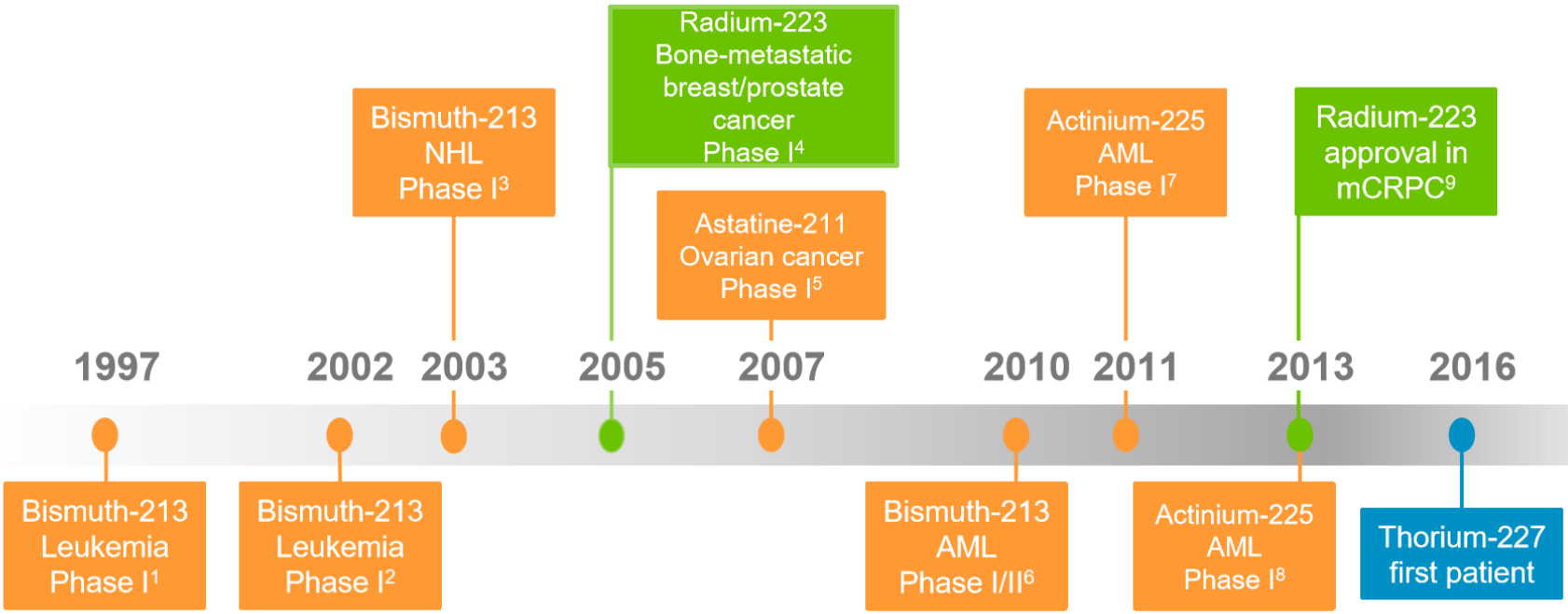
CARACTERÍSTICAS ESPECÍFICAS DE LA DOSIMETRÍA DE LOS RN

PERSPECTIVAS DE FUTURO DE LA TERAPIA CON RN ALFA

Evolving Interest in Alpha-Emitting Radionuclide Therapy

Advances in the targeted delivery of radionuclides and the increased availability of alpha emitters have led to a **number of recent clinical trials**[1]

Radium-223 is the only targeted alpha-emitter therapy approved for use in mCRPC[9]



The presented information is under investigation and has not been yet approved.

AML, acute myeloid leukemia; **mCRPC**, metastatic castration-resistant prostate cancer; **NHL**, non-Hodgkin's lymphoma.

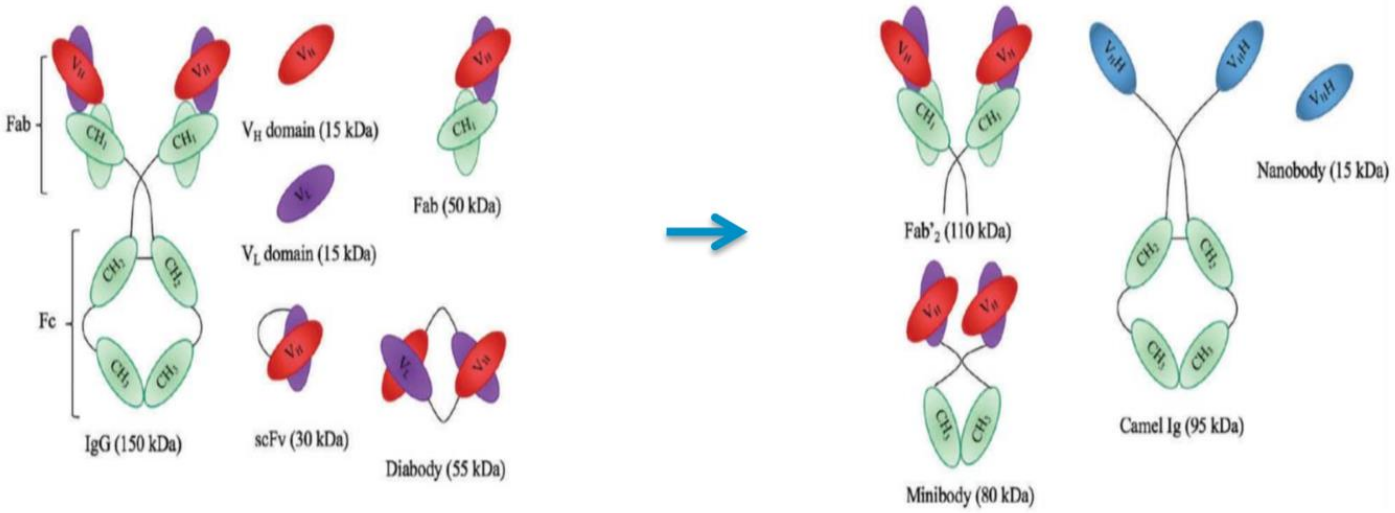
1. Jurcic JG *et al. Blood* 1997;90:2245. **2.** Jurcic JG *et al. Blood* 2002;100:1233–1239. **3.** Heeger S *et al. Abstr Pap Am Chem Soc* 2003;225:U261. **4.** Nilsson S *et al. Clin Cancer Res* 2005;11:4451–4459. **5.** Andersson H *et al. J Nucl Med* 2009;50:1153–1160. **6.** Rosenblat TL *et al. Clin Cancer Res* 2010;16:5303–5311. **7.** Jurcic JG *et al. J Clin Oncol* 2011;29:Abstract 6516. **8.** Jurcic JG *et al. Blood* 2014;124:5293. **9.** Xofigo (radium-223 dichloride) [summary product characteristics]. Bayer Pharma AG, Berlin, Germany. August 2017.

mAb-Mediated Targeted Alpha Therapy

mAb-mediated targeted alpha therapies bind potential tumor-associated antigen epitopes with high affinity.

High molecular weight and **Fc region** prolongs serum half-life (days or weeks).

- Smaller, engineered **mAb** derivatives clear the circulation rapidly and may penetrate tumors more effectively favorable tumor-background ratios.

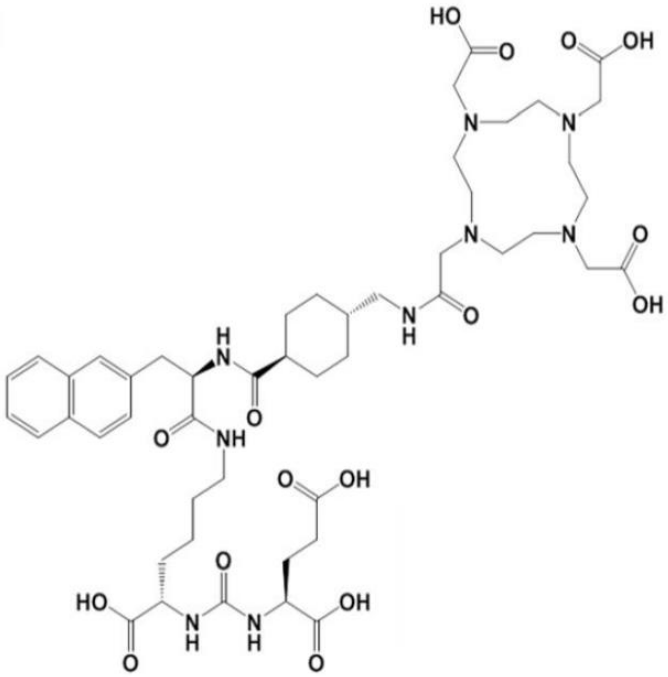


Dekempeneer Y *et al. Expert Opin Biol Ther* 2016;16:1035–1047.

Peptide- or Small-Molecule-Mediated Targeted Alpha Therapy

Ligands, synthetic protein scaffolds (e.g. affibodies), and substrate analogs (e.g. peptides) can be used as targeting agents[1]

PSMA-617[2]



1. Dekempeneer Y *et al. Expert Opin Biol Ther* 2016;16:1035–1047. 2. Umbricht CA *et al. EJNMMI Res* 2017;7:9.

Flexibility of Targeting Mechanisms Allows for a Wide Range of Applicability Across Tumor Types

Mechanism-mediated[1]

- Radium-223: Approved for use in metastatic prostate cancer in the bone; under investigation in multiple myeloma, bone-predominant metastatic breast cancer

Monoclonal antibody[1–5]

- Actinium-225: Under investigation in breast and ovarian cancer
- Astatine-211: Under investigation in glioblastoma
- Bismuth-213: Under investigation in multiple myeloma, ovarian cancer, and pancreatic cancer
- Thorium-227: Under investigation in NHL, gastric, colorectal, lung, ovarian, prostate, and breast cancers

Peptide or small molecule[1]

- Astatine-211: Under investigation in breast cancer
- Bismuth-213: Under investigation in Breast and ovarian carcinomas
- Actinium-225: Under investigation prostate cancer

1. Dekempeneer Y *et al. Expert Opin Biol Ther* 2016;16:1035–1047. **2.** Hammer S *et al.* Presented at: American Association for Cancer Research Annual Meeting; April 1–5, 2017; Washington, DC. **3.** Karlsson J *et al.* Presented at: American Association for Cancer Research Annual Meeting; April 1–5, 2017; Washington, DC. **4.** Hagemann UB *et al.* Presented at: American Association for Cancer Research Annual Meeting; April 1–5, 2017; Washington, DC. **5.** Cuthbertson A *et al.* Presented at: Annual Meeting of the European Society of Medical Oncology; October 7–11, 2016; Copenhagen, Denmark.

Ongoing Clinical Trials Examining Radium-223 in Combination with Novel Anti-Hormonal Agents

Trial	Endpoints	Population
Radium-223 + enzalutamide vs enzalutamide monotherapy PEACE III[1]	Radiographic PFS (overall survival secondary)	N=560 No second-generation ADT, no prior chemotherapy; asymptomatic/mildly symptomatic
Radium-223 + abiraterone acetate vs abiraterone acetate monotherapy ERA 223[2]	Symptomatic skeletal event–free survival (radiographic PFS, overall survival secondary)	N=806 No prior chemotherapy for CRPC; asymptomatic/mildly symptomatic

ADT, androgen deprivation therapy; **PFS**, progression-free survival.

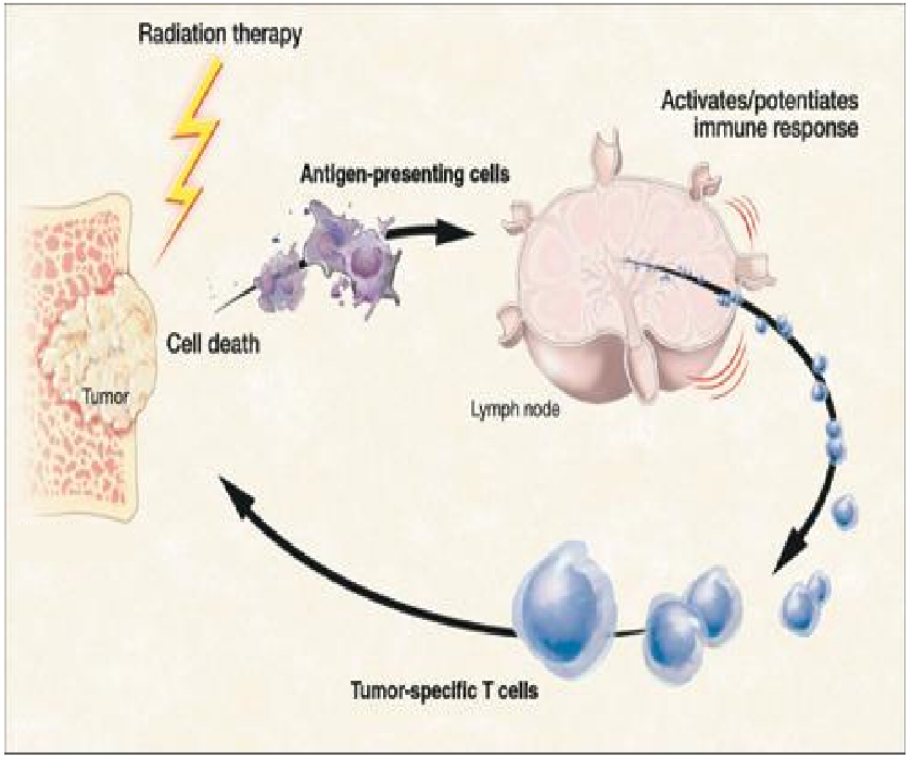
1. ClinicalTrials.gov. NCT02194842. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02194842. Accessed May 2017. **2.** ClinicalTrials.gov. NCT02043678. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02043678. Accessed May 2017. **3.** ClinicalTrials.gov. NCT01106352. Available at: https://www.clinicaltrials.gov/ct2/show/NCT01106352. Accessed May 2017.

Combination with Immuno-oncology Agents: Ionizing Radiation Induces Immunogenic Cancer Cell Death

Tumor cell death and secretion of signaling molecules by irradiation-stressed cells in the microenvironment promote immune cell activation[1]

Localized irradiation causes inflammation and normalization of tumor vasculature, allowing for T-cell infiltration[1]

Antigen from dying tumor cells can activate immune responses[2]

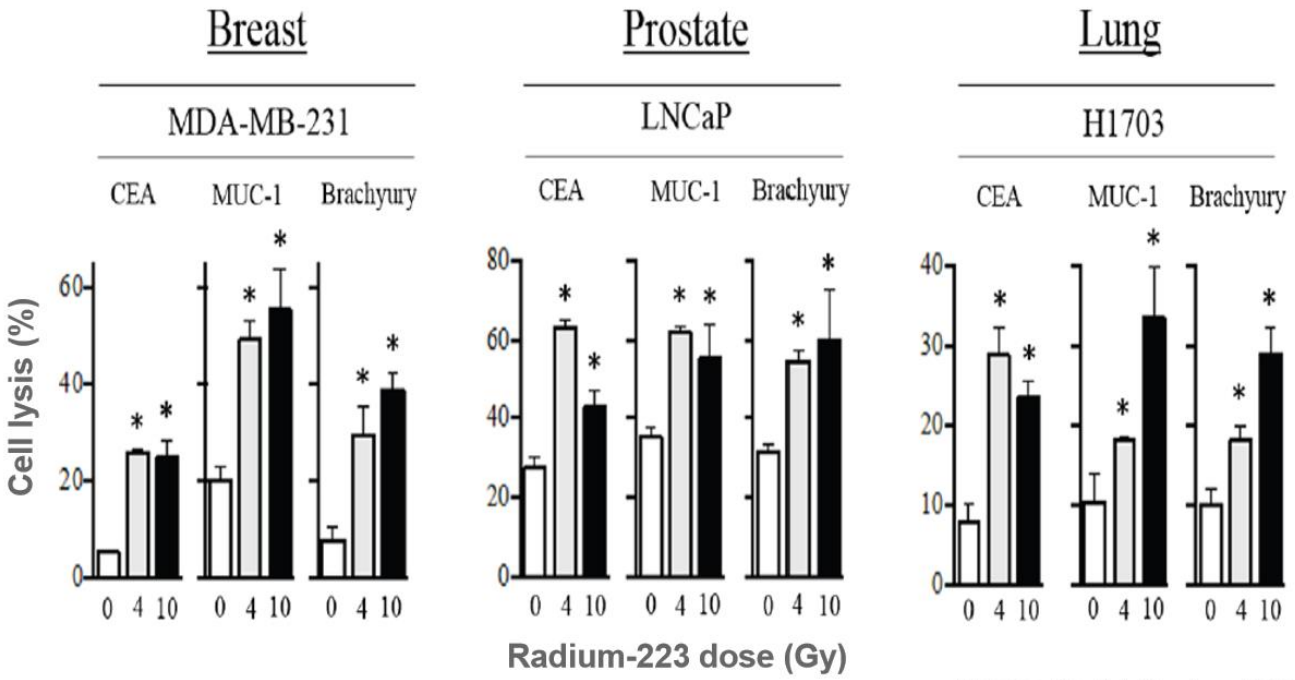


1. Eckert F *et al. Clin Transl Rad Oncol* 2017;2:29–35. **2**. Hodge JW *et al. Oncology* 2008;22:1064–1070.

Preclinical Work with Radium-223 Has Demonstrated the Potential for Creating an Immunostimulatory Environment

Radium-223 increased T-cell-mediated killing of carcinoma cell lines.

Sublethal exposure to radium-223 increases cytotoxic T lymphocyte–mediated lysis



Malamas SA *et al. Oncotarget* 2016; 7:86937–86947.

Targeted Alpha Therapy: Work in Progress

	Radium-223 (Bayer)	Thorium-227 (Bayer)	Actinium-225 (Actinium Pharmaceuticals; Fusion Pharmaceuticals)	Lead-212 (Areva)
Approvals	Prostate cancer	–	–	–
Clinical development	Prostate cancer • Radium-223 + abiraterone (Phase III)[1] • Radium-223 + enzalutamide (Phase III)[2] • Radium-223 + atezolizumab (Phase Ib)[3] • Radium-223 + pembrolizumab (Phase II)[4] • Radium-223 + niraparib (Phase I)[5] Breast cancer (Phase II)[6–8] Multiple myeloma (Phase I)[9] Renal cell carcinoma (Phase I)[10]	NHL (Phase I)[11]	Leukemia and myelodysplastic syndrome (Phase I)[12]	HER2-expressing cancers (Phase I)[13]
Half-life	11.4 days	18.7 days	10 days	10.6 hours

AML, acute myeloid leukemia; **HER2**, human epidermal growth factor receptor 2; **NSCLC**, non-small cell lung cancer.

1. ClinicalTrials.gov. NCT02194842. **2.** ClinicalTrials.gov. NCT02043678. **3.** ClinicalTrials.gov. NCT02814669. **4.** ClinicalTrials.gov. NCT03093428. **5.** ClinicalTrials.gov. NCT03076203. **6.** ClinicalTrials.gov. NCT02258464. **7.** ClinicalTrials.gov. NCT02258451. **8.** ClinicalTrials.gov. NCT02366130. **9.** ClinicalTrials.gov. NCT02928029. **10.** ClinicalTrials.gov. NCT02880943. **11.** ClinicalTrials.gov. NCT02581878. **12.** ClinicalTrials.gov. NCT00672165. **13.** ClinicalTrials.gov. NCT01384253.

Targeted α-Therapy of Metastatic Castration-Resistant Prostate Cancer with ^{225}Ac-PSMA-617: Dosimetry Estimate and Empiric Dose Finding

J Nucl Med 2017

Clemens Kratochwil[1], Frank Bruchertseifer[2], Hendrik Rathke[1], Marcus Bronzel[3], Christos Apostolidis[2], Wilko Weichert[4], Uwe Haberkorn[1,5], Frederik L. Giesel[1], and Alfred Morgenstern[2]

[1]Department of Nuclear Medicine, University Hospital Heidelberg, Heidelberg, Germany; [2]Directorate for Nuclear Safety and Security, European Commission, Joint Research Centre, Karlsruhe, Germany; [3]ABX-CRO, Dresden, Germany; [4]Institute of Pathology, University Hospital at Technical University Munich, Munich, Germany; and [5]Cooperation Unit Nuclear Medicine, German Cancer Research Center (DKFZ), Heidelberg, Germany

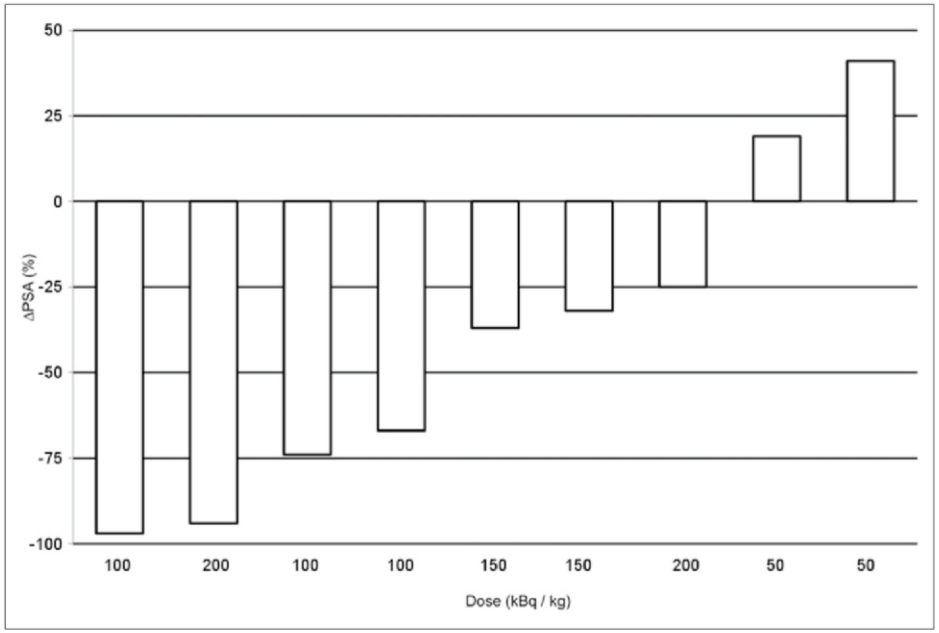


FIGURE 4. Waterfall graph of PSA response in evaluable patients. PSA response was observed in 75% of patients. No dose–response correlation was observed the 100–200 kBq/kgBW treatment activities.

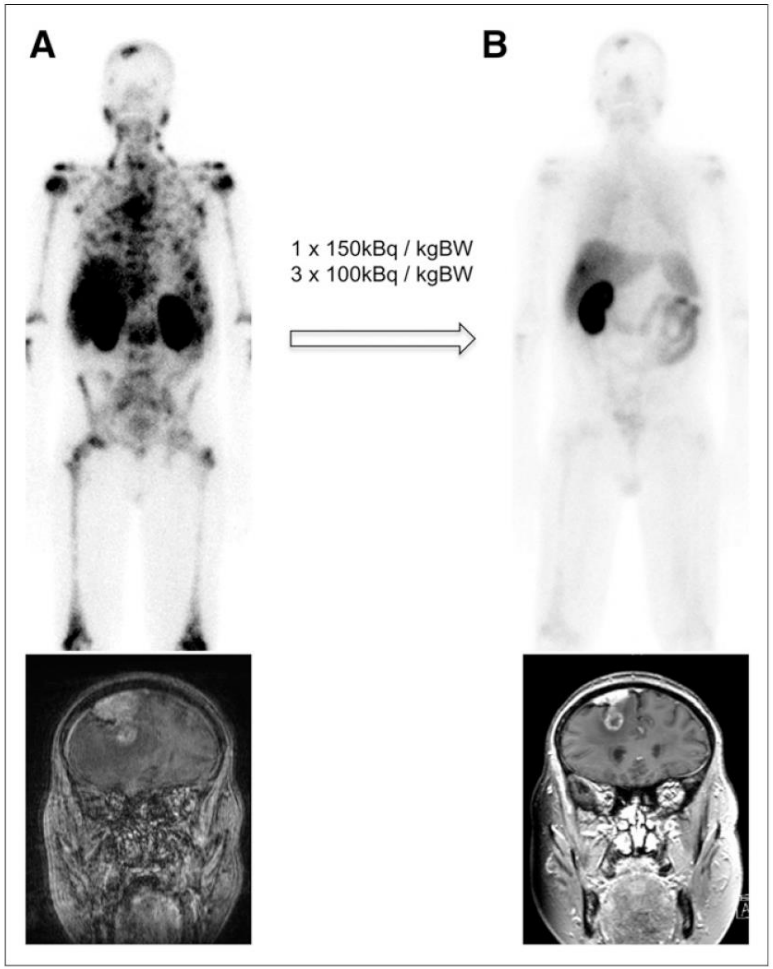


FIGURE 2. (A) At baseline, a patient presented with diffuse-type red marrow infiltration visualized with ^{99m}Tc-MIP1427 PSMA scintigraphy (top) and brain metastasis (bottom). (B) Imaging follow-up 8 mo later presented partial response in bone (top) and brain (bottom).

CONSIDERACIONES FINALES

Los radiofármacos son medicamentos que requieren del mismo procedimiento de aprobación que los fármacos no radiactivos

Los emisores alfa presentan un excelente perfil para tratar muy selectivamente las lesiones diana con baja toxicidad a los tejidos sanos

Ra223 es el primer emisor alfa autorizado para el tratamiento del cáncer en humanos

Ra223 es seguro y eficaz para el tratamiento del CPRC
Estan en fase de ensayo pre-clínico o clínico diversos radiofármacos marcados con otros radionúclidos alfa y Fases III con Ra223 en combinación con otros fármacos o en distinta secuenciación terapéutica

CONSIDERACIONES FINALES

La dosimetría personalizada es una necesidad clínica para determinar la irradiación a las lesiones diana o a los tejidos sanos

Parece muy complejo y poco realista determinar la dosis de radiofármaco en base a estudios de farmacocinética y famacodinámica aplicados a todos los pacientes

En el proceso de aprobación como medicamento se pueden determinar los perfiles dosimétricos genéricos que podrán individualizarse tras obtener imágenes pre y post-terapéuticas con los propios emisores alfa o con emisores gamma con la misma biodistribución