4th Research Forum of the
European Association for palliative care

Scientific Evidence of Radionuclides in Palliative Care

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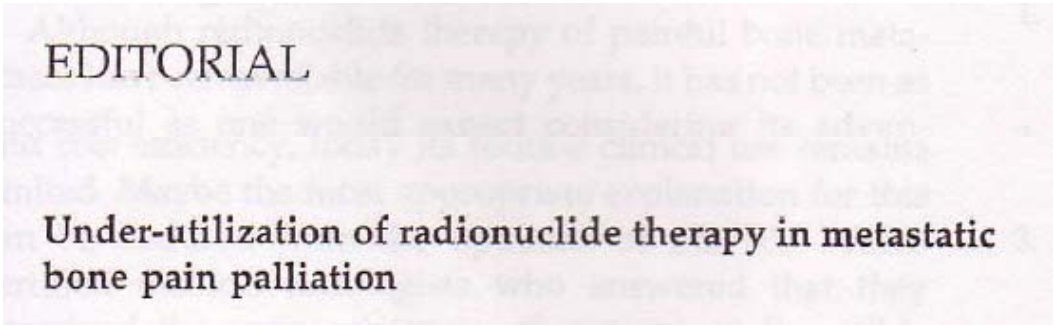
- Introduction



EDITORIAL

Under-utilization of radionuclide therapy in metastatic bone pain palliation

F. PONS, Nucl Med Commun 2002

«It is our mission as nuclear medicine specialists, to be able to convince our clinicians of the advantages of this kind of therapy and primarily identify which patients can best obtain the therapeutic benefits »

Scientific Evidence of Radionuclides in Palliative Care

Current use of radionuclides in bone pain palliation

- How does it work?
- Which results?

Perspectives

- High LET radionuclides
- Repeated injections
- Association with chemotherapy
- Association with external beam radiotherapy
- Association with biphosphonates

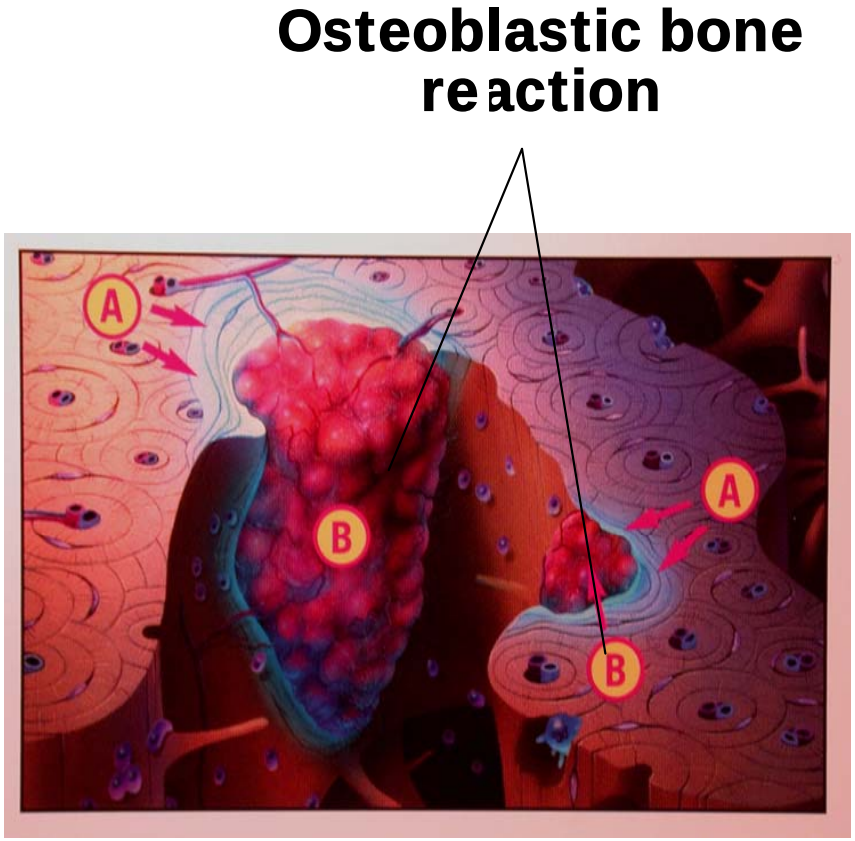
How does it work?

Specific bone uptake of the radiopharmaceutical proportionally to osteoblastic bone turnover

Decay of radionuclide
ie: ^{153}Sm or ^{89}Sr

➔ β particles emission

=> electrons interactions with perimetastatic bone and metastatic lesions

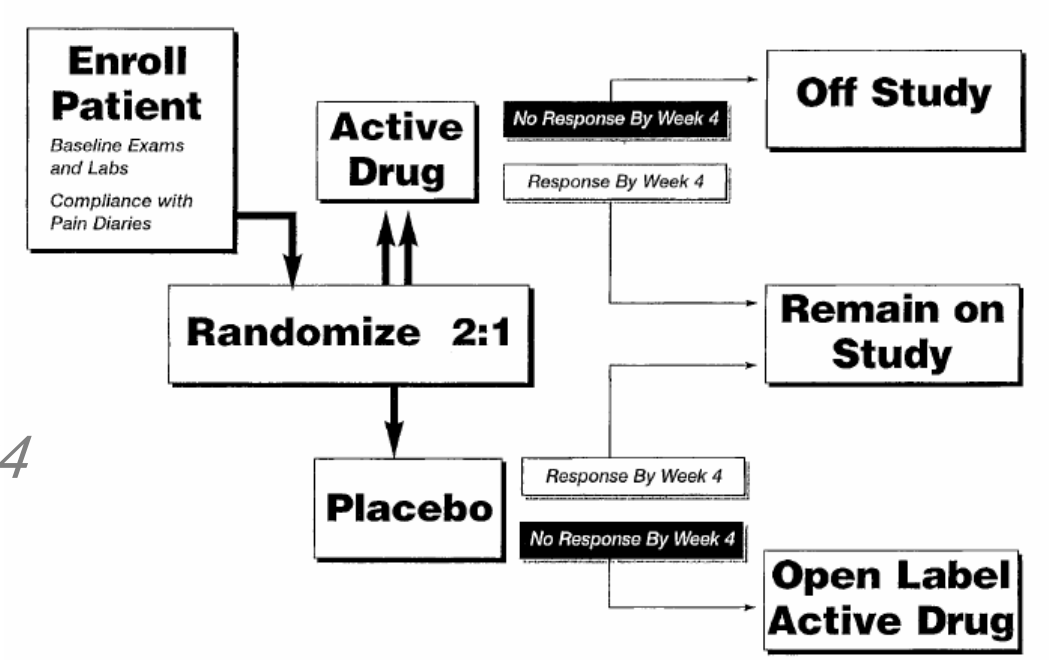


- **How does it work?**

Which radiopharmaceuticals are available?

Quadramet®	Metastron®	Re-bone®
Samarium-153-EDTMP	Strontium-89	Rhenium-186-HEDP
Eβ = 0.233 MeV Eγ = 103 keV	Eβ = 1,463 MeV	Eβ = 1.07 MeV Eγ = 137 keV
1.93 days	50 days	3.7 days
Bone : 3.1 mm Soft tissue : 0.6 mm	Bone : 8.0 mm Soft tissue : 2.4 mm	Bone : 5.0 mm Soft tissue : 1.1 mm

Which results?

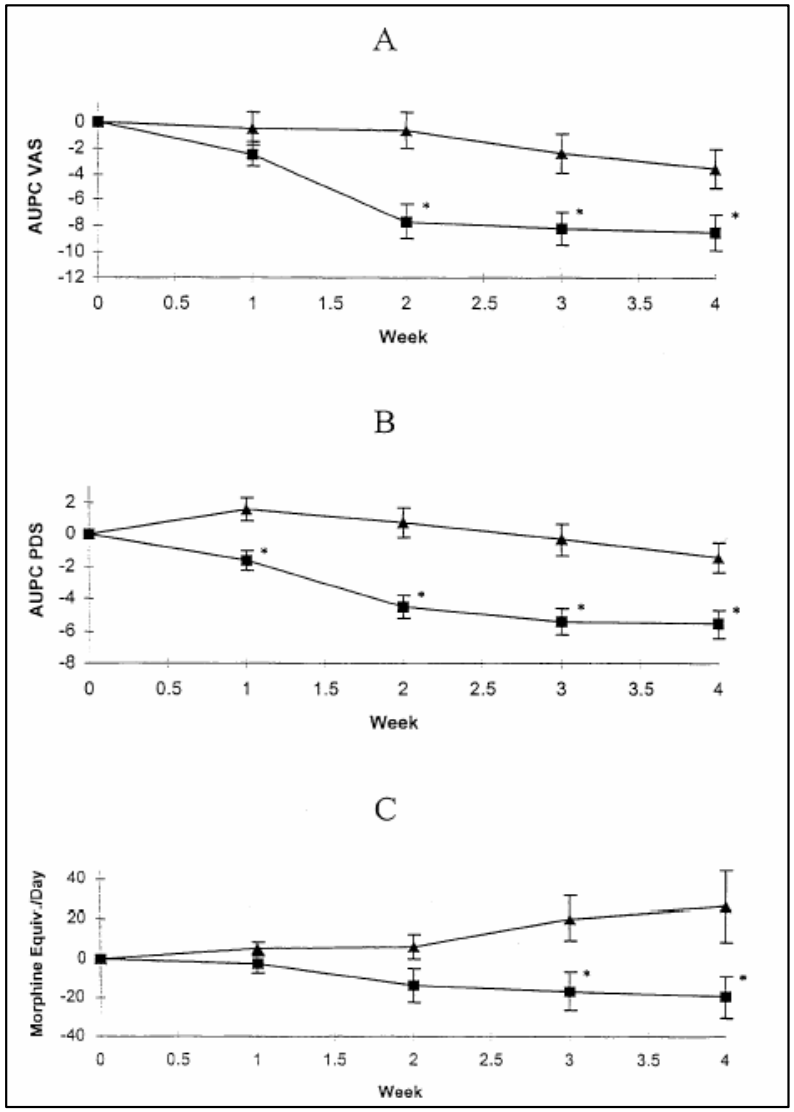


Sartor O, et al. Urology. 2004

- Analgesic consumption measured daily
- Pain measured by patient using VAS and pain descriptor scale recorded twice daily in the diary

➢ Stastistical analysis done on «area under curve» sums

▪ Which results?



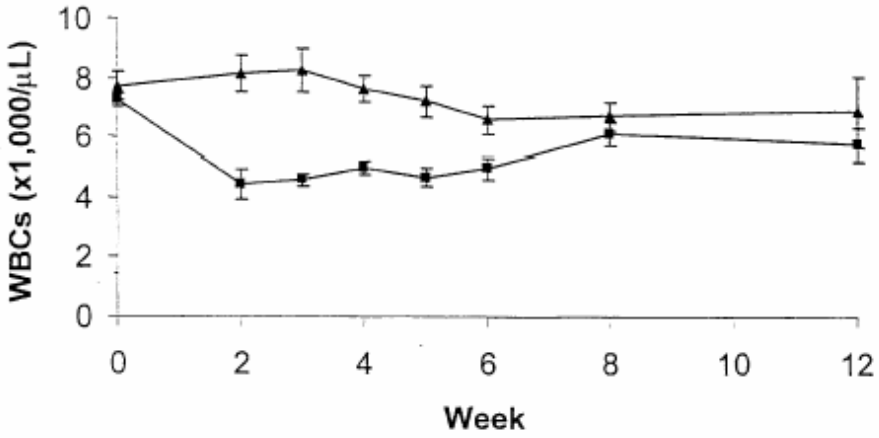
A - Area under pain curve for VAS

B - Area under pain curve for PDS

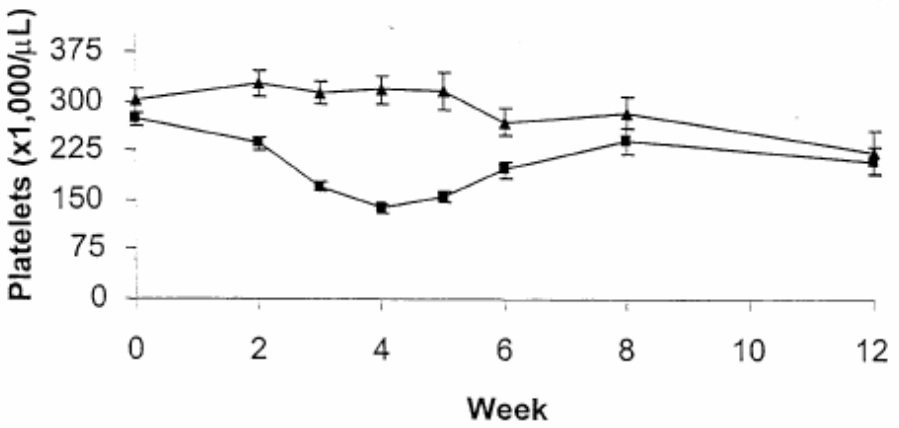
C - Change in opioïd analgesic use

Sartor O, et al. Urology. 2004

- **Which results?**



WBC



Platelets

Sartor O, et al. Urology. 2004

Which results?

Authors (Year)	Design of Trial	N° of patients	Primary Cancer	KPS	Activity	Response (%)		Duration of response Range or	Flare pheno--menon (%)
						Pain Relief	Including Complete Response		
Turner(1989)[98]	U, Mo	35	Various		10.36-31.08 MBq/kg	65%	14.3%	6 to 35 w	
Turner(1991)[99]	U, Mo	23	Various			61%		4 to 40 w	
Farhangi (1992)[100]	Es, Mo	22	Various		18.5-111 MBq/kg	65.4%		1 to 11 mo	18
Collins (1993)[101]	Es, Mo	52	Prostate	PS ≥ 3 (0-4)	18.5-111 MBq/kg	76%		1 to 8.8 mo	12
Ahonen (1994)[102]	Es, Mu	35	Various		4-19 MBq/kg	80%	54%	2 to 17 w	5.7
Deng (1995) [103]	U, Mo	136	Various		18.5-≥37 MBq/kg	92.6%	49%		
Resche (1997)[96]	RC, DB, Mu	114	Various	≥40	18.5-37 MBq/kg	70%	33%	1 to >16 w	11
Sartor (1997)[115]	RC, DB, Mu	152	Prostate	≥50	37 MBq/kg	Reduction of pain and opiate use		>16w	
Serafini (1998)[97]	RC, DB, Mu	118	Various	≥40	18.5-37 MBq/kg	62%	31%	2 to 12 mo	10

KPS : Karnofsky Performance Status ; Es : Escalating dose trial ; RC : Randomised Controlled ;
U : Uncontrolled ; Mu : Multicentre ; Mo : Monocentre w : weeks ; mo : months
Various: prostate, breast, lung,

Which results?

Predictors of palliative response for samarium Sm-153 lexidronam: Analysis of data from three randomized controlled blinded trials.

ASCO 2006 Prostate Cancer Symposium

Serafini AN, et al. J Clin Oncol. 1998
Resche I, et al. Eur J Cancer. 1997
Sartor O, et al. Urology. 2004

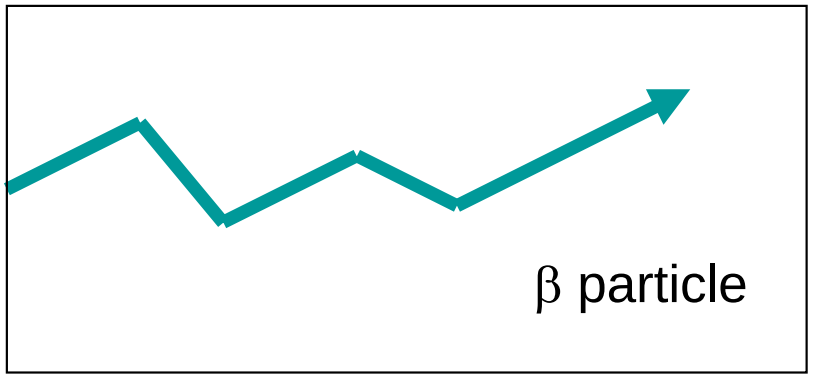
- Analysis of variables potentially predictive of response
  - baseline Hemoglobin level
  - absolute administered activity
  - skeletal retention and baseline creatinine

➢ No particular subset of pts potentially eligible for Sm-153 treatment can be deemed unlikely to respond to therapy

High LET radionuclides

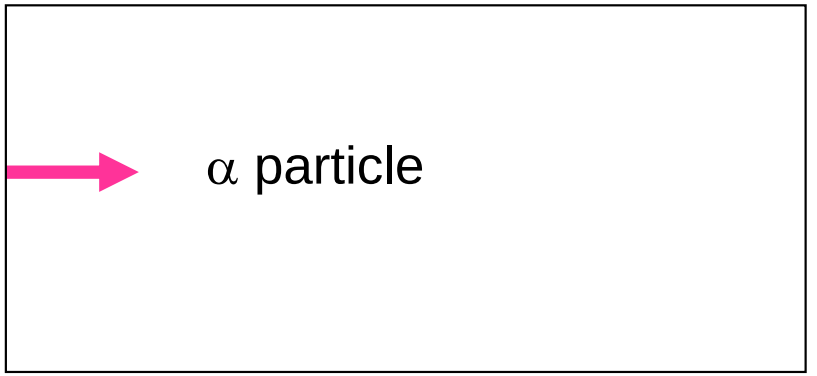
- **β Emitters – low LET**

  Low antitumoral efficiency
  Range: a few mm
  Toxicity = limitation regarding injected activities



- **α Emitters – high LET**

  Range 100 μm
  Potentially more efficient
  Potentially less myelotoxic



- **High LET radionuclides**

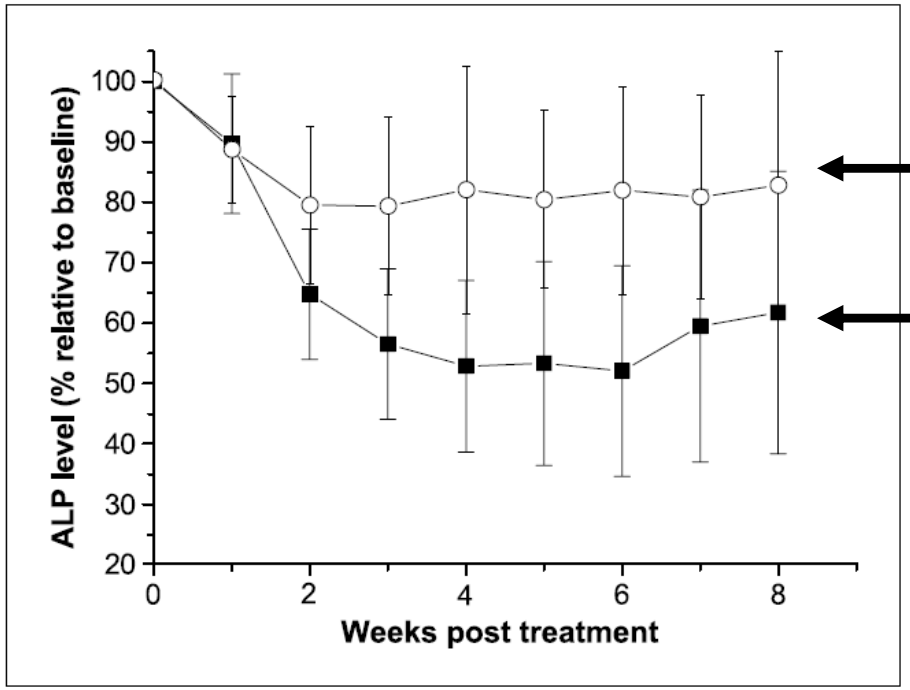
First Clinical Experience with α-Emitting Radium-223 in the Treatment of Skeletal Metastases

Sten Nilsson,[1] Roy H. Larsen,[2] Sophie D. Fosså,[3] Lise Balteskard,[4] Kari W. Borch,[2] Jan-Erik Westlin,[5] Gro Salberg,[2] and Øyvind S. Bruland[2,3]

- 15 prostate – 10 breast cancer patients
- ^{223}Ra single injection - dosage escalating study design
- EORTC QLC-C 30 questionnaire
- Decrease in pain score >10 in more than 50% of patients
- W8: improvement 56%, unchanged 24%, worse 20%)
- Platelets: grade 1 - n= 1 / Neutrophiles: grade 3 – n= 2

Nilsson S, et al
Clin Cancer Res. 2005

High LET radionuclides



Breast cancer

Prostate cancer

Serum alkaline phosphatase level at baseline and after ^{223}Ra administration

- Decrease in 52% / 29% in prostate and breast cancer patients respectively

Nilsson S, et al
Clin Cancer Res. 2005

- **Repeated injections**

Repeated Bone-Targeted Therapy for Hormone-Refractory Prostate Carcinoma: Randomized Phase II Trial With the New, High-Energy Radiopharmaceutical Rhenium-188 Hydroxyethylidenediphosphonate

By Holger Palmedo, Agnieska Manka-Waluch, Peter Albers, Ingo G.H. Schmidt-Wolf, Michael Reinhardt, Samer Ezziddin, Alexius Joe, Roland Roedel, Rolf Fimmers, F.F. Knapp Jr, Stefan Guhlke, and Hans-Jürgen Biersack

- 64 HRPC patients randomized
  - Groupe A – single injection
  - Groupe B – 2 injections (intervall – 8 weeks)

- **Repeated injections**

	Gpe A	Gpe B
Response rate	60%	92%
Duration of pain relief	2.55	5.66
PSA Decrease	7%	39%
Median time to progression	4.3 months	7.0 months
Median overall survival time	7.0 months	12. months

Palmedo H, et al
J Clin Oncol. 2003

Association with chemotherapy

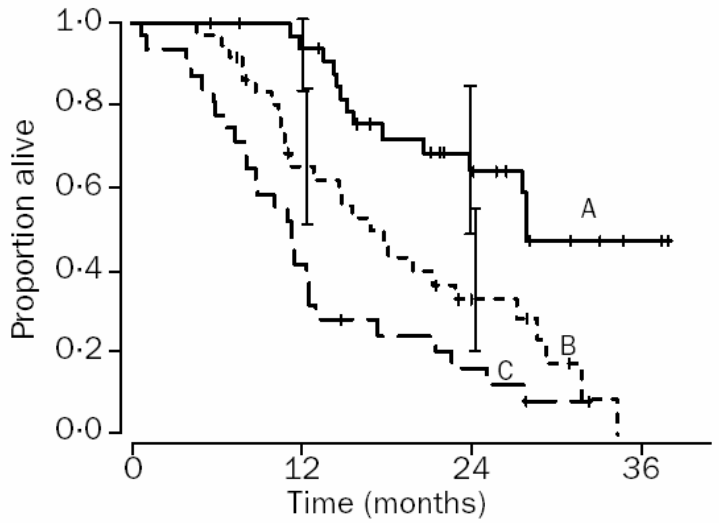
Bone-targeted therapy for advanced androgen-independent carcinoma of the prostate: a randomised phase II trial

Shi-Ming Tu, Randall E Millikan, Bayabel Mengistu, Ebrahim S Delpassand, Robert J Amato, Lance C Pagliaro, Danai Daliani, Christos N Papandreou, Terry L Smith, Jeri Kim, Donald A Podoloff, Christopher J Logothetis

- 103 patients with prostate cancer
- Induction chemotherapy
- Randomisation of patients (n = 72) with stable or responding disease to consolidation therapy
  - =>Doxorubicin alone
  - =>Doxorubicin + ^{89}SR

Tu S, et coll
Lancet 2001

Association with chemotherapy



A) Doxorubicin and Sr-89	36	35	34	26	21	15	5	3	0
B) Doxorubicin alone	36	35	27	18	7	7	3	0	0
C) Not randomised	31	26	17	8	6	4	1	0	0

Kaplan-Meier estimates of overall survival

- Médian survival

17.5 months for all 103 patients
27.7 months for patients with Sr89 + doxorubicin
16.8 months for patients with doxorubicin alone

Tu S, et coll
Lancet 2001

Association with chemotherapy

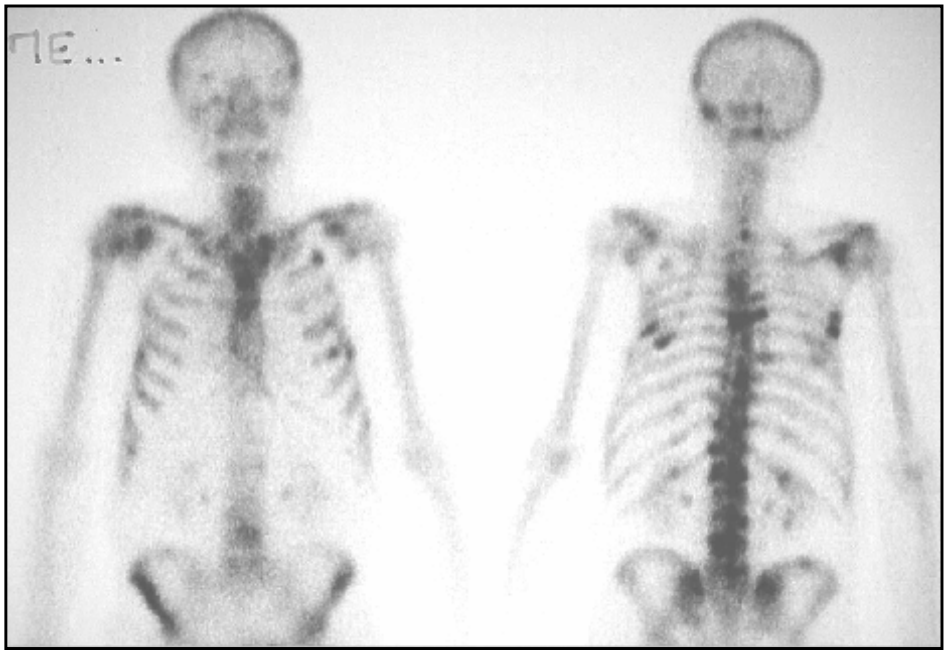
Sciuto R et al.
Effects of low-dose cisplatin on ^{89}Sr therapy for painful bone metastases from prostate cancer: a randomized clinical trial.
J Nucl Med. 2002 Jan;43(1):79-86.

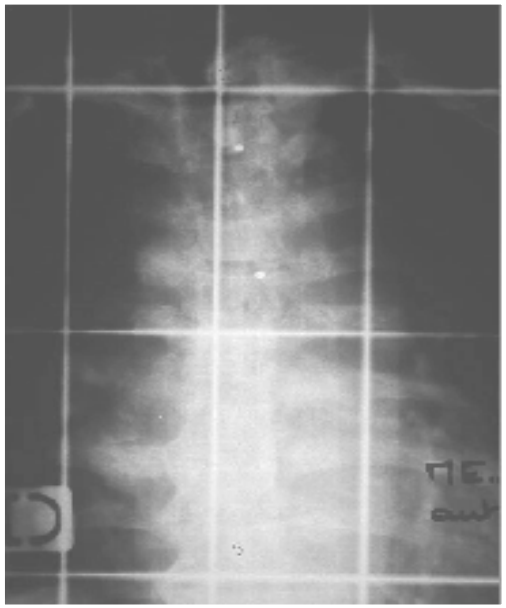
70 pts with metastatic hormone-refractory prostate cancer

Arm A: 148 MBq ^{89}Sr + 50 mg/m^2 cisplatin,
Arm B 148 MBq ^{89}Sr + placebo.

- Overall pain relief 91% and 63% ($p < 0.01$)
- Median duration 120 d and 60 d ($p = 0.002$).
- New painful sites: 14% / 30% ($P = 0.18$).
- Bone disease progression: 27% - 64% ($p = 0.01$).
- Median global survival 9 mo and 6 mo ($p = 0.30$).

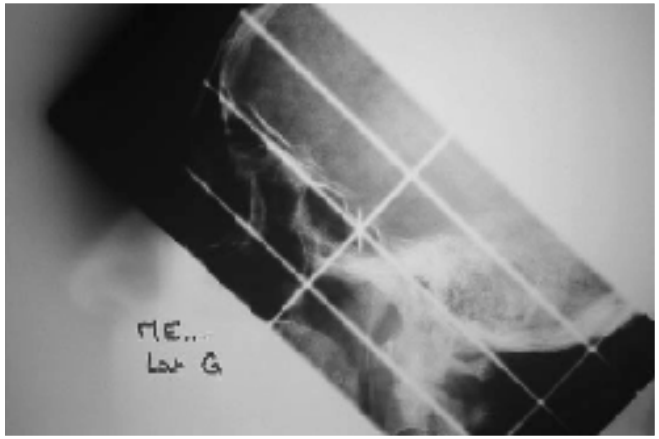
Association with external beam radiotherapy





24Gy – T8-T9

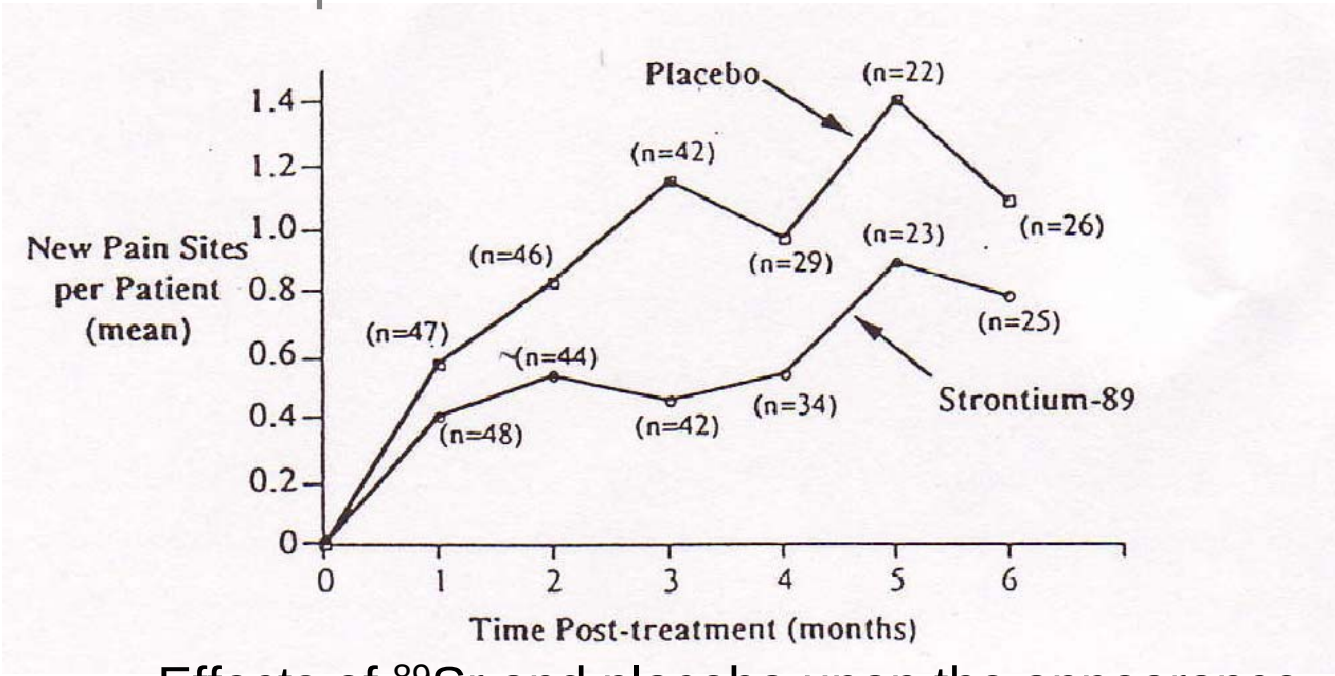
- April - Quadramet®
- June - Quadramet®
- August EBRT
- Oct - Quadramet®
- Jan - EBRT



12 Gy – Skull base

Association with external beam radiotherapy

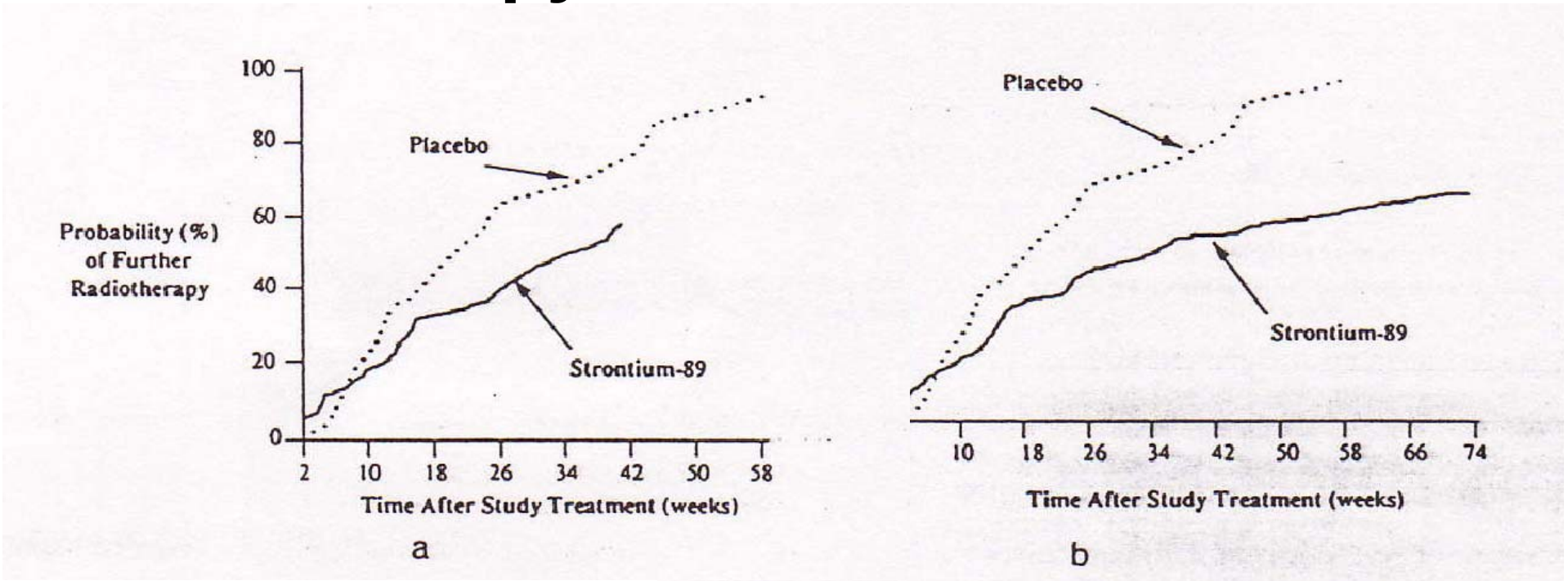
n = 126 prostate cancer patients
EBR + (^{89}Sr OR Placebo) (randomisation)
3 months: 59% / 34% (active group / placebo group) are free of new painful metastases



Effects of ^{89}Sr and placebo upon the appearance of new sites of pain over time

Porter AT, et coll
Int J Radiat Oncol Biol Phys 1993

Association with external beam radiotherapy



Actuarial analysis of time to further radiotherapy
to any osseous lesion (a) and to a new site of pain (b)

- Over the 4 months, more patients in the active group have a greater than 50% reduction in PSA and alkaline phosphatase ($p<0.01$)

Porter AT, et coll
Int J Radiat Oncol Biol Phys 1993

- **Association with biphosphonates**

Combined therapy of Sr-89 and zoledronic acid in patients with painful bone metastases

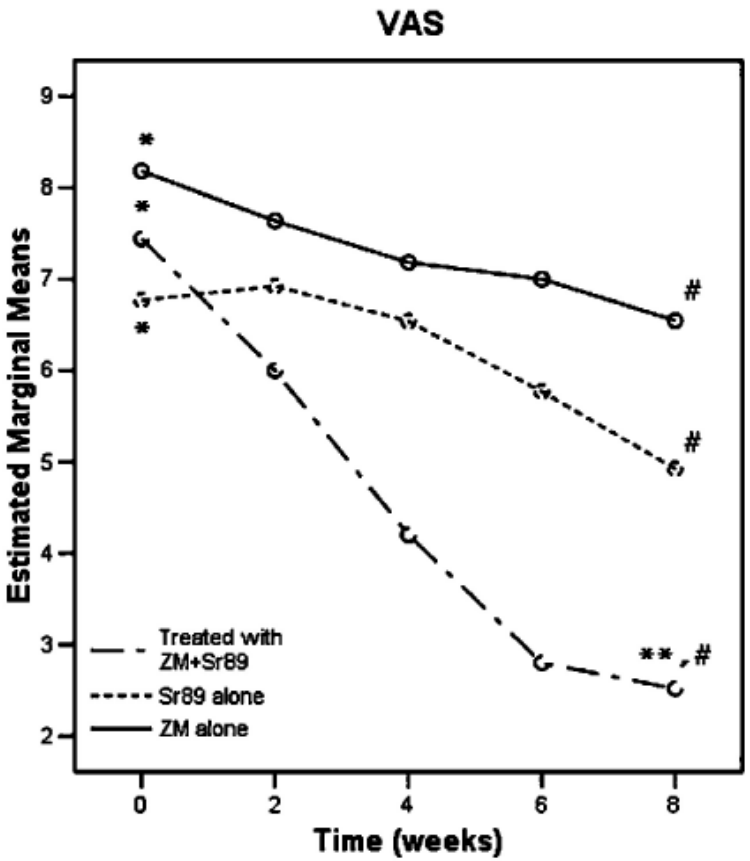
Giovanni Storto [a,b,d,*], Michele Klain [b], Gaetano Paone [b], Raffaele Liuzzi [a], Leonardo Molino [c], Alfredo Marinelli [c], Andrea Soricelli [e], Leonardo Pace [b], Marco Salvatore [b,d]

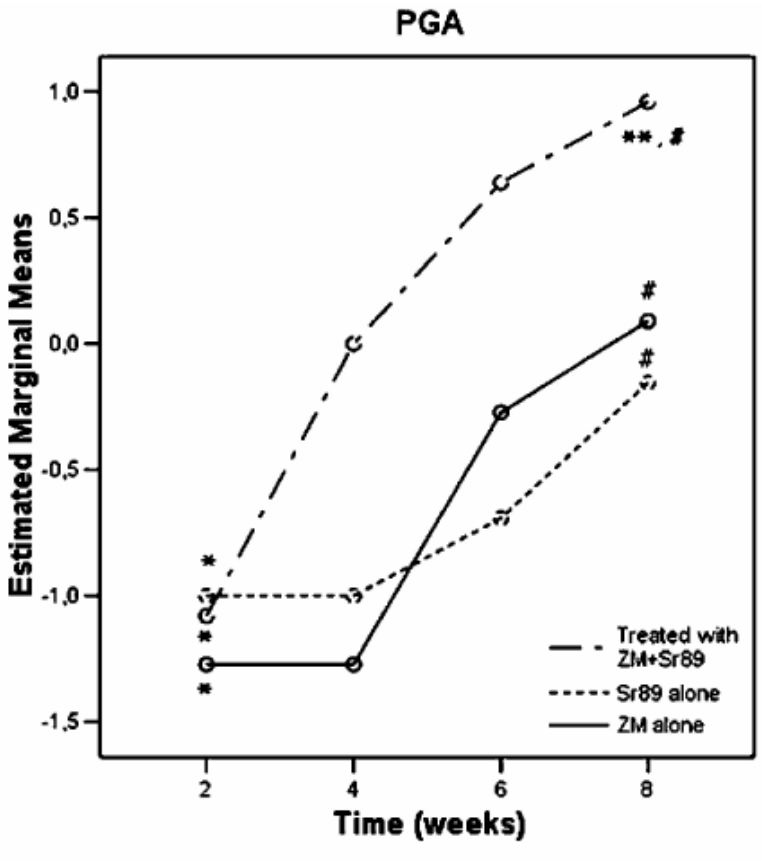
Gpe: ZM + ^{89}Sr (n = 25)
Gpe B: ZM (n = 11)
Gpe C: ^{89}Sr (n = 13)

- Assesment of pain score (VAS)
- Assessment of general clinical condition

Storto G, et al
Bone. 2006

Association with biphosphonates





Storto G, et al
Bone. 2006 Jan 21

Conclusion

PAIN PALLIATION

- Scientific evidence of efficacy of radionuclide therapy
- Need for a pluridisciplinary approach

ANTITUMORAL EFFICIENCY

- A serious expectation!