

Dosimetria delle lesioni scheletriche e valutazione del carico di malattia

a cura di:

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Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori"
Istituto di Ricovero e Cura a Carattere Scientifico

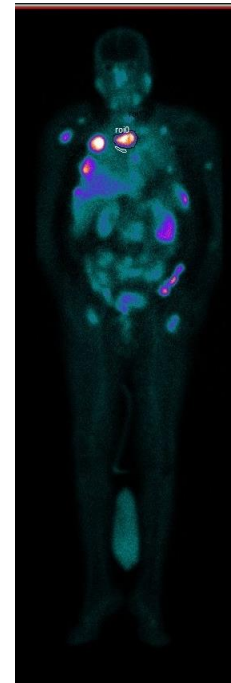
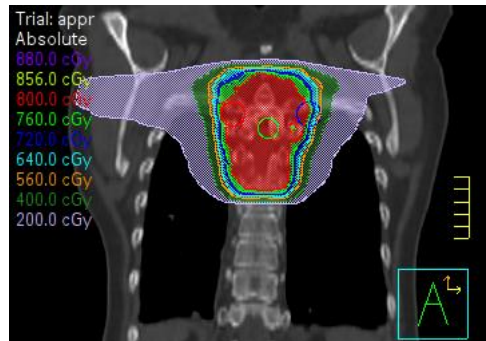
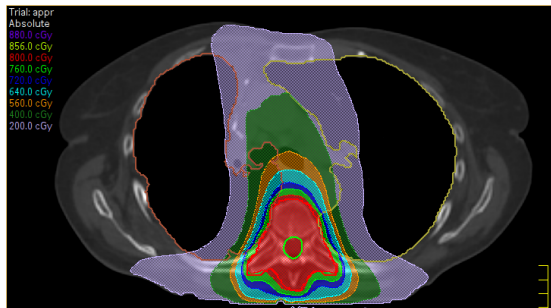
ISTITUTO
ROMAGNOLO
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DEI TUMORI
DINO AMADORI

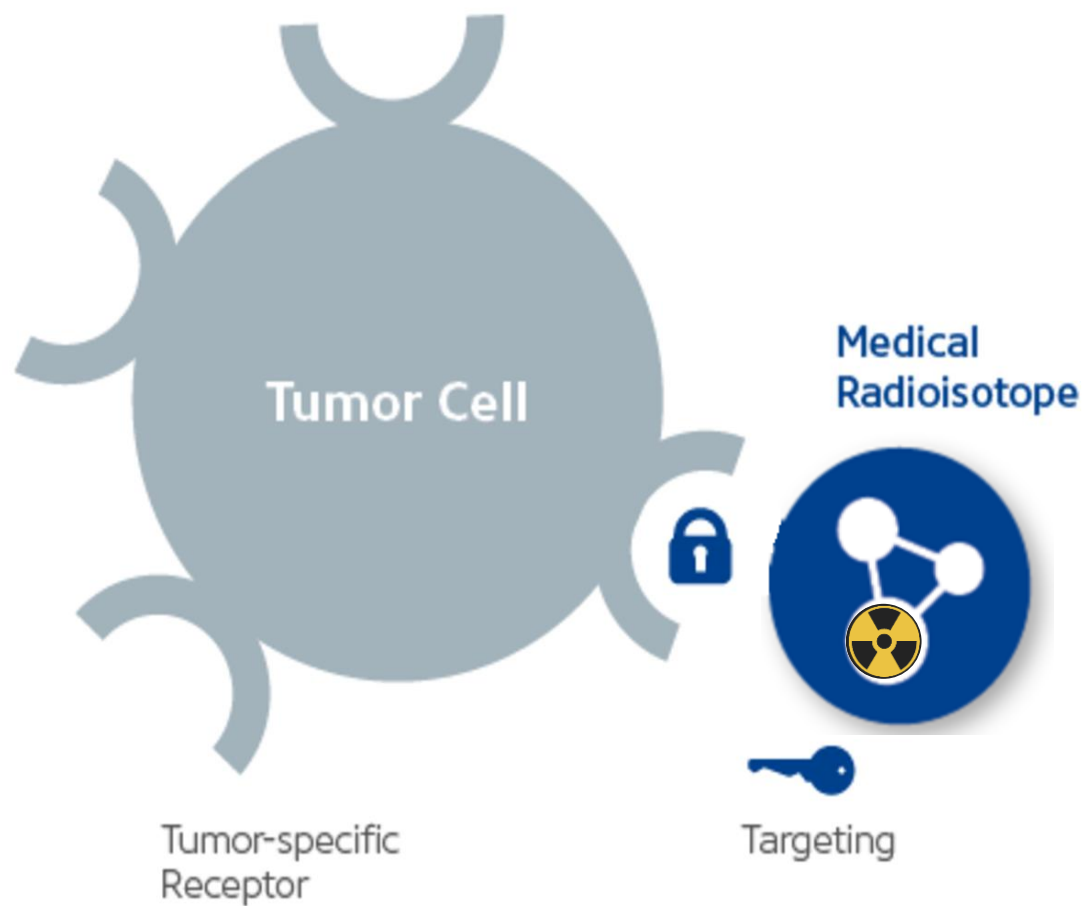
VII CONGRESSO NAZIONALE
SOCIETÀ ITALIANA DI OSTEONCOLOGIA
20-21 OTTOBRE 2022 ROMA
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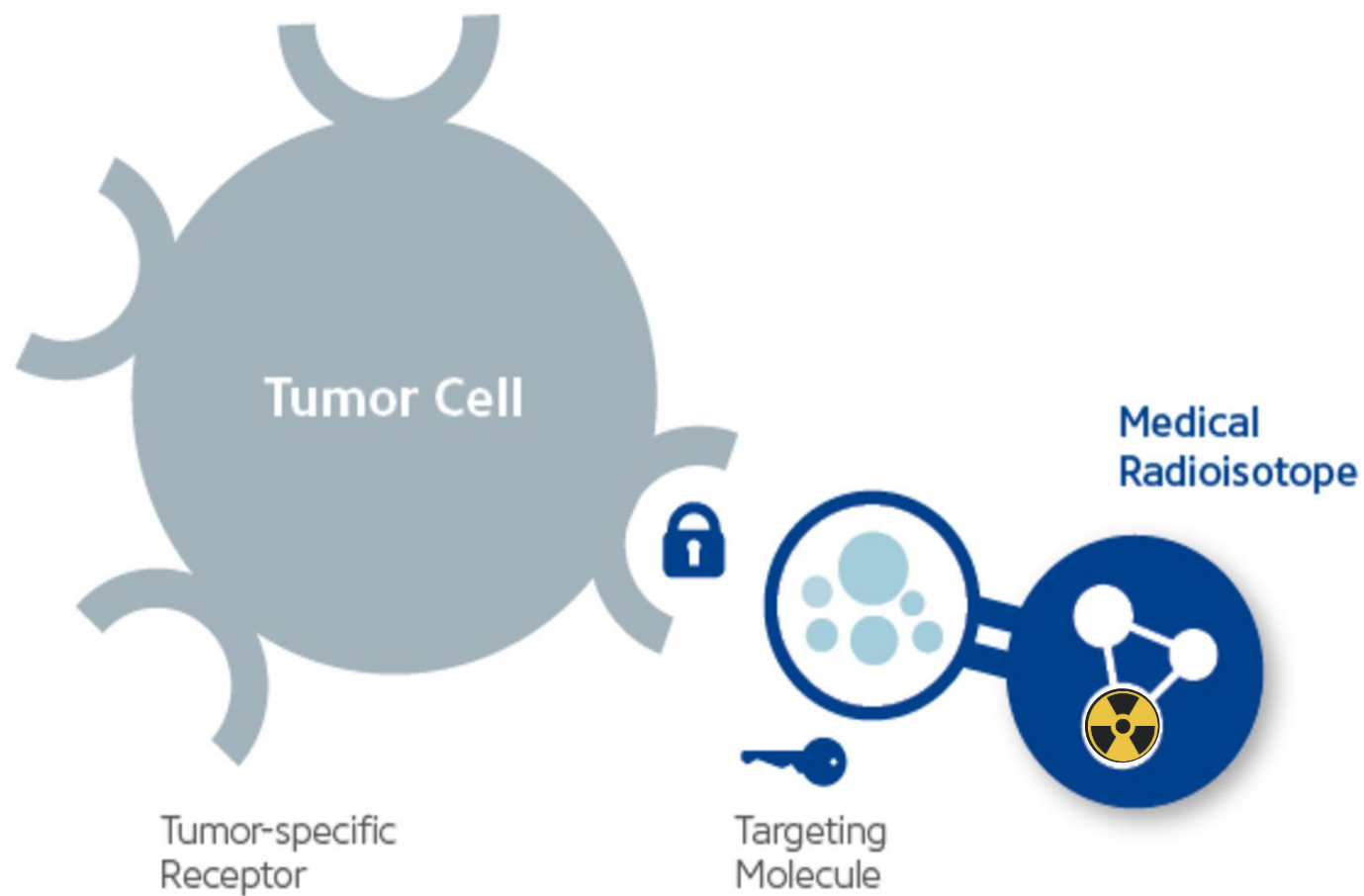
Nei pazienti affetti da lesioni scheletriche spesso è presente un quadro di malattia diffusa caratterizzato da lesioni multiple.

Le opzioni terapeutiche con radiazioni ionizzanti sono

- ✓ Radioterapia a fasci esterni → trattamento localizzato, spesso antalgico
- ✓ Terapia radiometabolica → trattamento sistemico







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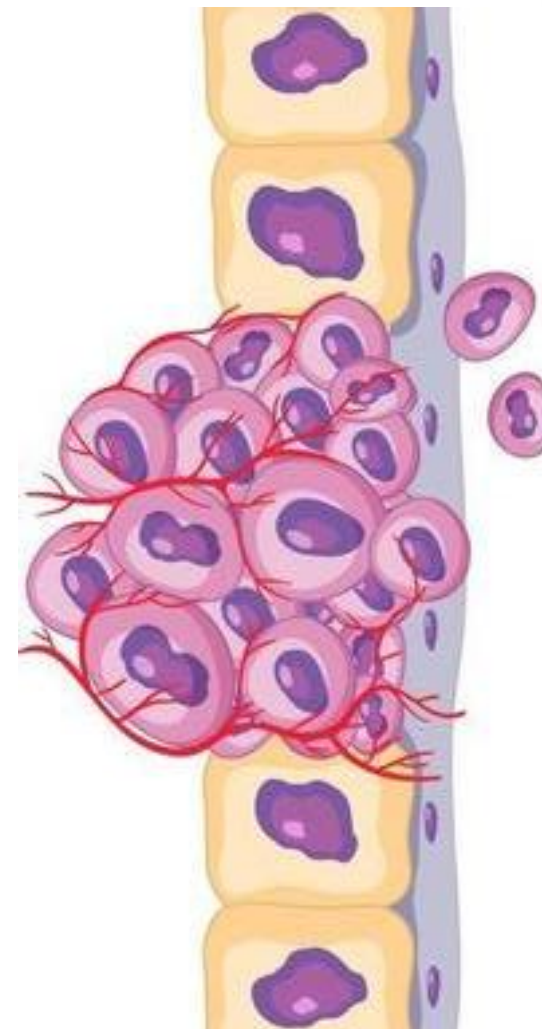
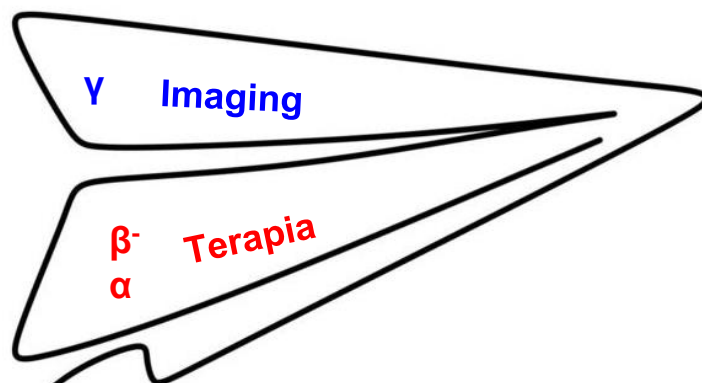
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Teragnostica = **θεραπεία** + **γνώσις**
(therapeía) (gnòsis)
[terapia] [conoscenza]

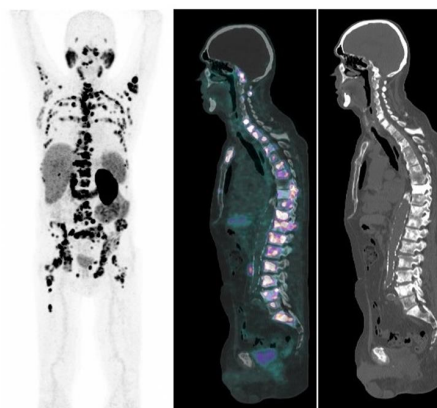




You treat what you see
You see what you treat

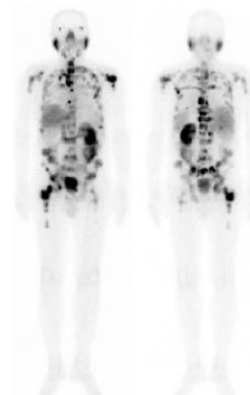
PET – basale

⁶⁸Ga-PSMA



Post terapia - 1° ciclo

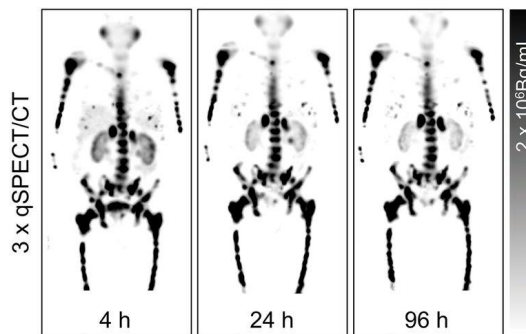
¹⁷⁷Lu-PSMA



Paganelli et al (EJNMMI 2020, 47(13):3008–3017)



If you measure
you can optimize

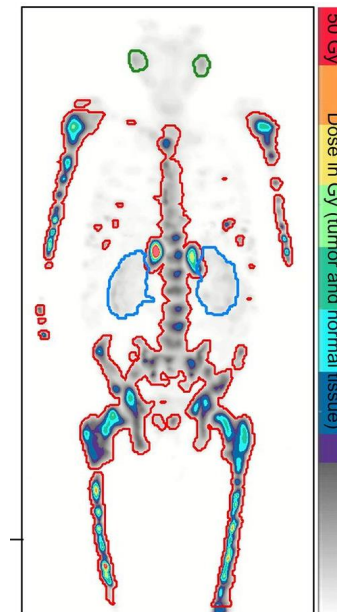


$$\text{Dose assorbita [Gy]} = \frac{\text{energia}}{\text{massa}}$$



Effetto biologico

Violet et al (JM 2013, 60(4):517–523)

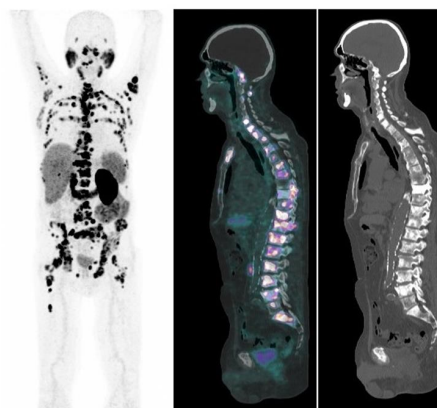




You treat what you see
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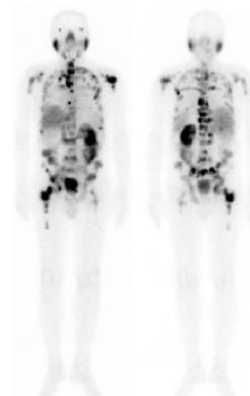
PET – basale

⁶⁸Ga-PSMA



Post terapia - 1° ciclo

¹⁷⁷Lu-PSMA



Paganelli et al (E.INMMI 2020, 47(13):3008–3017)

→ Medicina personalizzata



If you measure
you can optimize

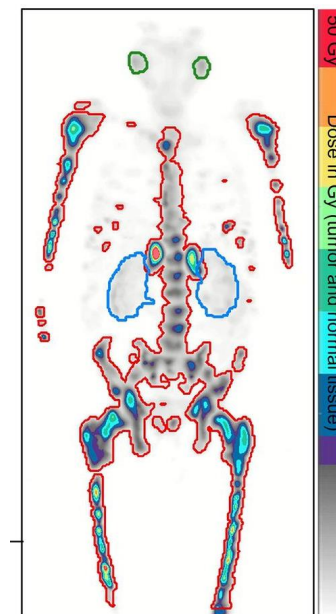


$$\text{Dose assorbita [Gy]} = \frac{\text{energia}}{\text{massa}}$$



Effetto biologico




Violet et al (JM 2013, 60(4):517–523)



Lesioni multiple diffuse → ottimale un trattamento sistemico

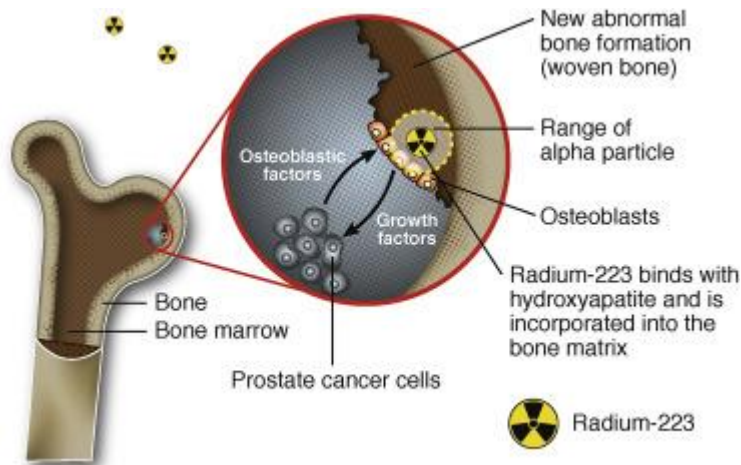
Per questo tipo di pazienti la terapia radiometabolica rappresenta una valida opzione

Radiofarmaci maggiormente utilizzati

Radiofarmaco	T1/2 fisico	Emissione per Terapia	Range in acqua/tessuto	Posologia	Dosimetria post terapia
89-Sr 	50.5 d	β^- $E_{Max} = 1.46 \text{ MeV}$	$R_{max}=8\text{mm}$ $R_{medio}=2.4\text{mm}$	148 MBq (4 mCi) Via endovenosa (1-2 min)	NA
153-Sm 	1.93 d	β^- $E_{Max} =$ 0.64 MeV (30%), 0.71 MeV (50%), 0.81 MeV (20%) $E_{media} = 0.233 \text{ MeV}$	$R_{max}=3 \text{ mm}$ $R_{medio}=0.6 \text{ mm}$	37 MBq/kg Via endovenosa (1-2 min)	Parziale γ 29% SPECT (103 keV)
223-Ra 	11.43 d	95.3% α 3.6% β^-	$R_{medio}=$ 0.05-0.08 mm	55 kBq/kg Orale 6 cicli, ogni 4 settimane	Parziale γ <1.1% SPECT (82 e 154 keV)
177Lu-PSMA	6.65 d	100% β^- $E_{Max} =$ 0.50 MeV (76%), 0.39 MeV (9.7%), 0.18 MeV (12%)	$R_{max}=2 \text{ mm}$ $R_{medio}=0.7 \text{ mm}$	4.4–5.5–7.4 GBq Via endovenosa (20 min)	Sì Emissioni γ SPECT (208 keV o 113 keV)

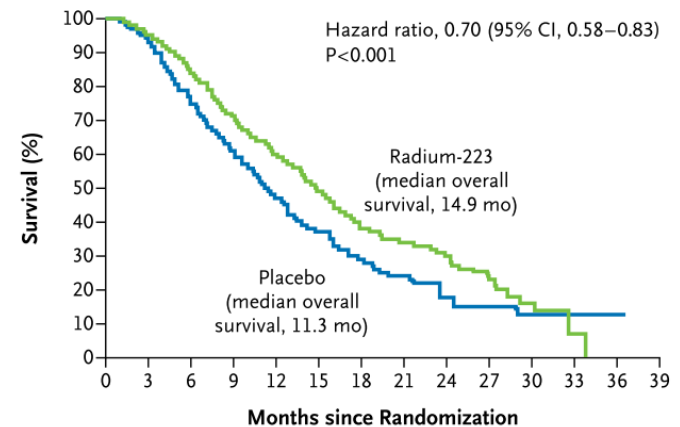
^{223}Ra

- Calciomimetico → segue la fisiologia di uptake del calcio
- Emettitore alfa → high LET (Linear Energy Transfer), Double-strand DNA breaks, short range (<100µm)
- Per lesioni ossee



Cha et al (*J Formos Med Assoc* 2017, 116(11):825–836)

A Overall Survival



No. at Risk

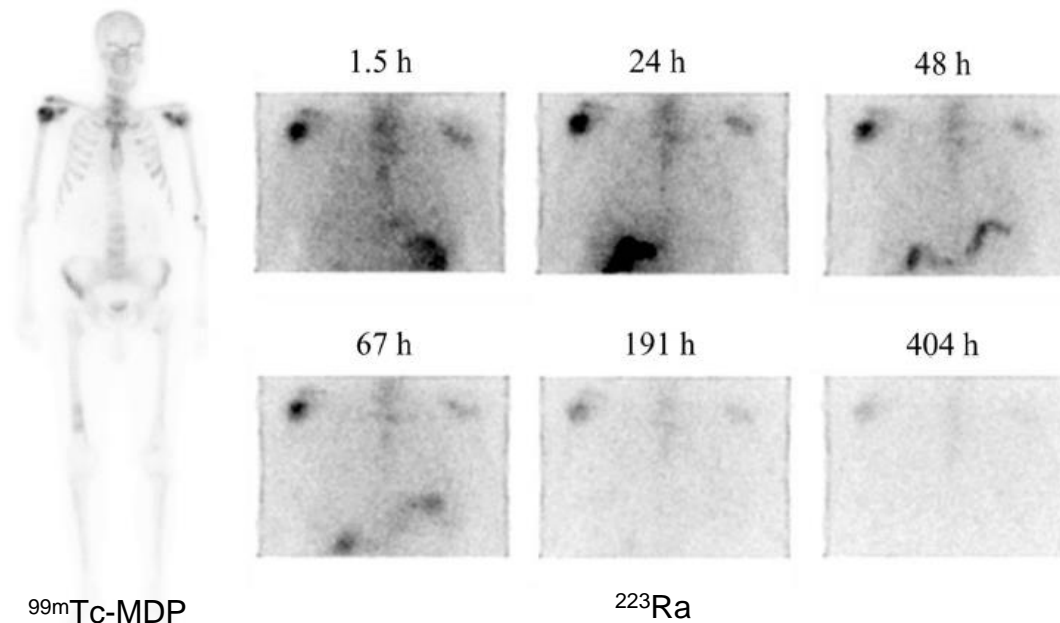
Radium-223	614	578	504	369	274	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	103	67	39	24	14	7	4	2	1	0

ALSYMPCA Study phase III trial

Parker et al (*NEJM* 2013, 369(3):213–223)

^{223}Ra

- Calciomimetico → segue la fisiologia di uptake del calcio (canali sodio-potassio)
- Emettitore alfa → high LET (Linear Energy Transfer), Double-strand DNA breaks, short range (<100µm)
- Per lesioni ossee

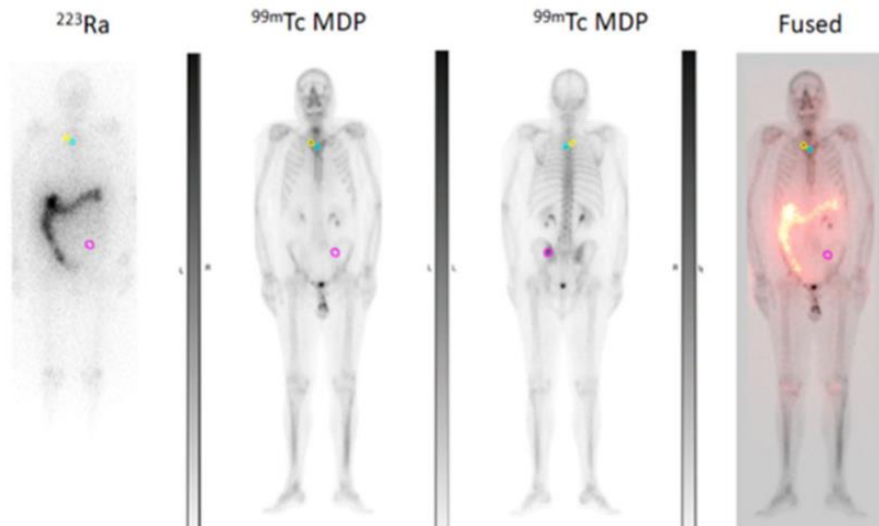


Pacilio et al (EJNMMI 2016, 43(1):21-33)

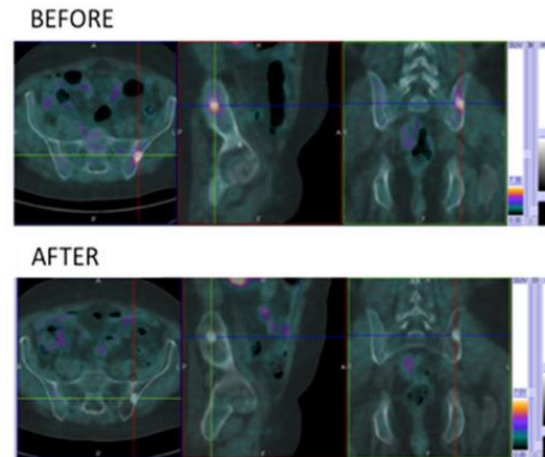
^{223}Ra

The understanding of the physical and biologic factors that impacts response and toxicity in non-target tissues is essential to avoid the risk that α -emitters may be abandoned before they have been properly tested in the clinic.

- 5 mCRCP
- 55 kBq/kg – max 6 cys – 4 wks interval
- $^{99\text{m}}\text{Tc}$ MDP + ^{223}Ra planar images
- Blood samples for chromosome damage (Dicentric and Micronuclei)



^{18}F —choline PET/CT

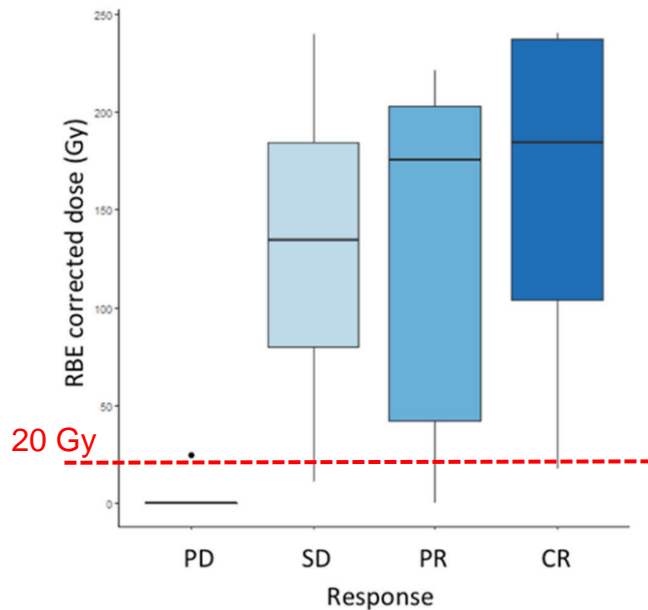


Sciuto et al (*J Exp Clin Canc Res* 2021, 10:281)

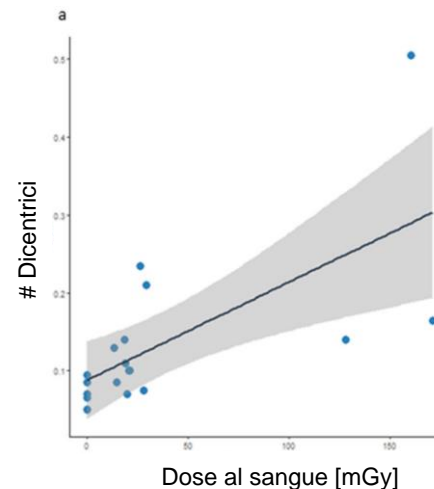
^{223}Ra

The understanding of the physical and biologic factors that impacts response and toxicity in non-target tissues is essential to avoid the risk that α -emitters may be abandoned before they have been properly tested in the clinic.

- 5 mCRCP - 20 lesions
- 55 kBq/kg – max 6 cys – 4 wks interval
- $^{99\text{m}}\text{Tc}$ MDP + ^{223}Ra planar images
- Blood samples for chromosome damage (Dicentric and Micronuclei)

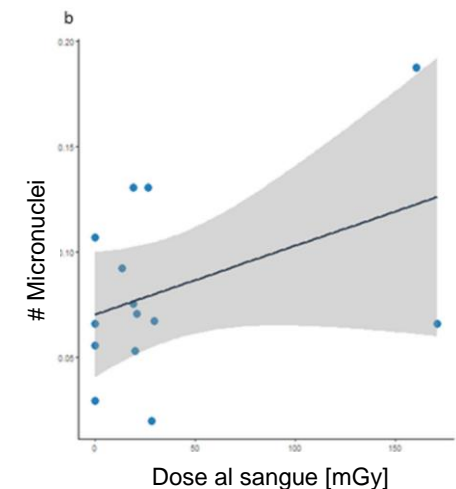


Sciuto et al (J Exp Clin Canc Res 2021, 10:281)



cor = 0.66
p-value= 0.003

Radiation-specific
damage



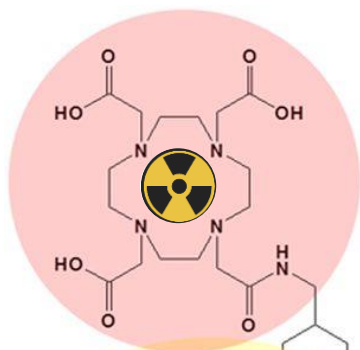
cor = 0.41
p-value= 0.14

NON Radiation-specific
damage

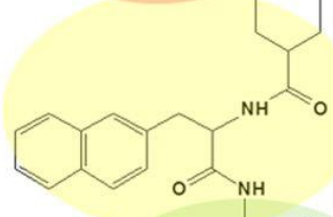
^{177}Lu -PSMA

PSMA = Prostate Specific Membrane Antigen

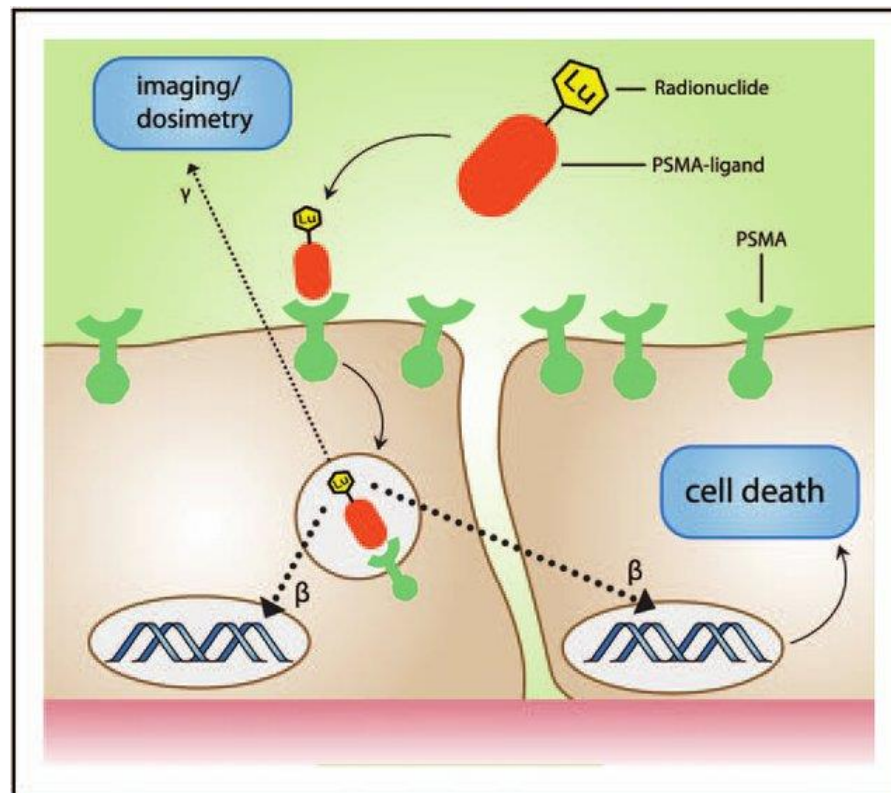
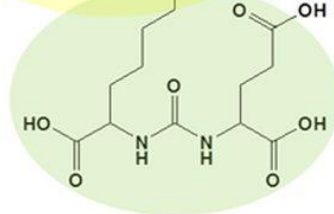
Anello chelante



Linker



Carrier o vettore
(PSMA-617)

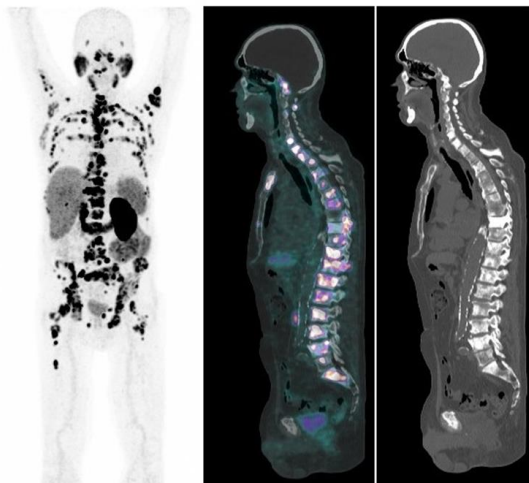


Kratochwil et al, JNM 2016; 57 (8) 1170-1176

Ferdinandus et al (Curr Opin Urol 2018, 28:197–204)

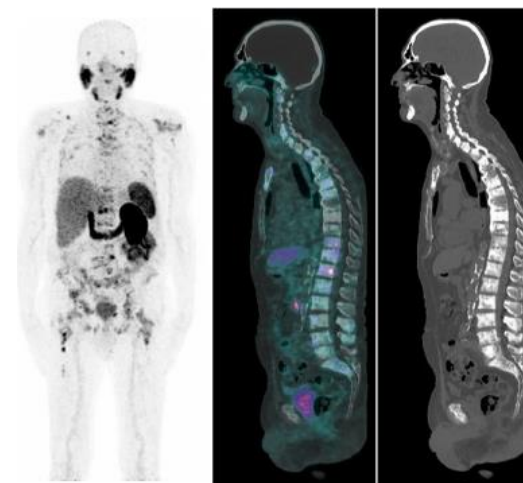
PET – basale

⁶⁸Ga-PSMA



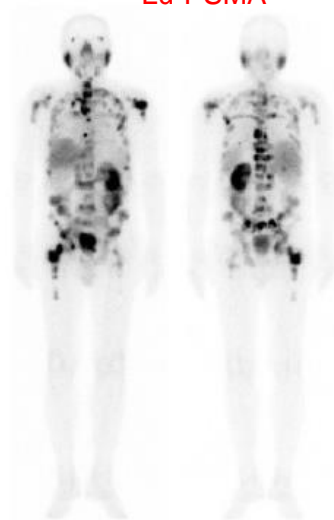
PET – 4° ciclo

⁶⁸Ga-PSMA



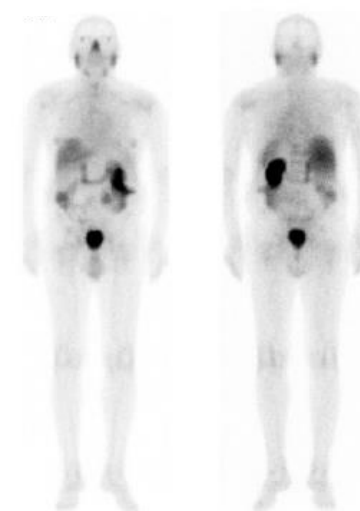
Whole body - 1° ciclo

¹⁷⁷Lu-PSMA



Whole body - 4° ciclo

¹⁷⁷Lu-PSMA

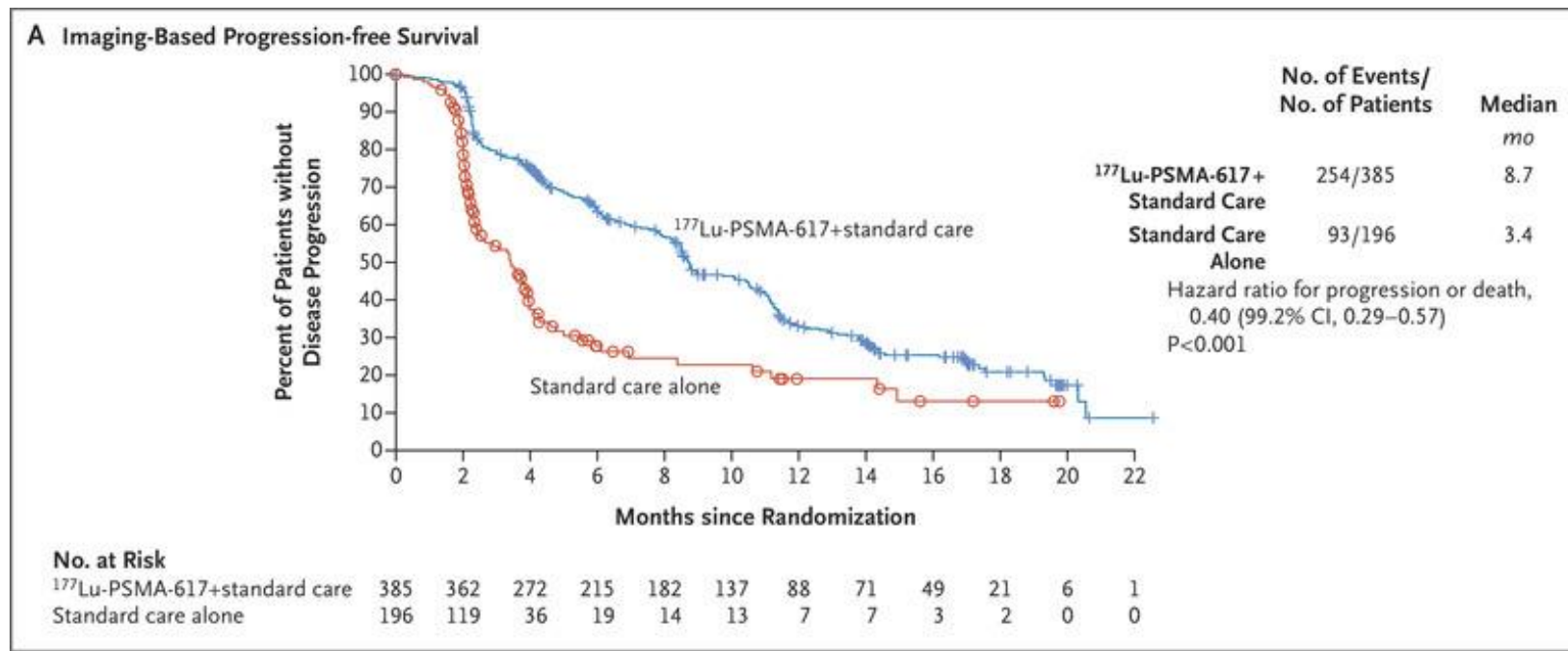


Paganelli et al (EJNMMI 2020, 47(13):3008–3017)

ORIGINAL ARTICLE

Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

O. Sartor, J. de Bono, K.N. Chi, K. Fizazi, K. Herrmann, K. Rahbar, S.T. Tagawa,

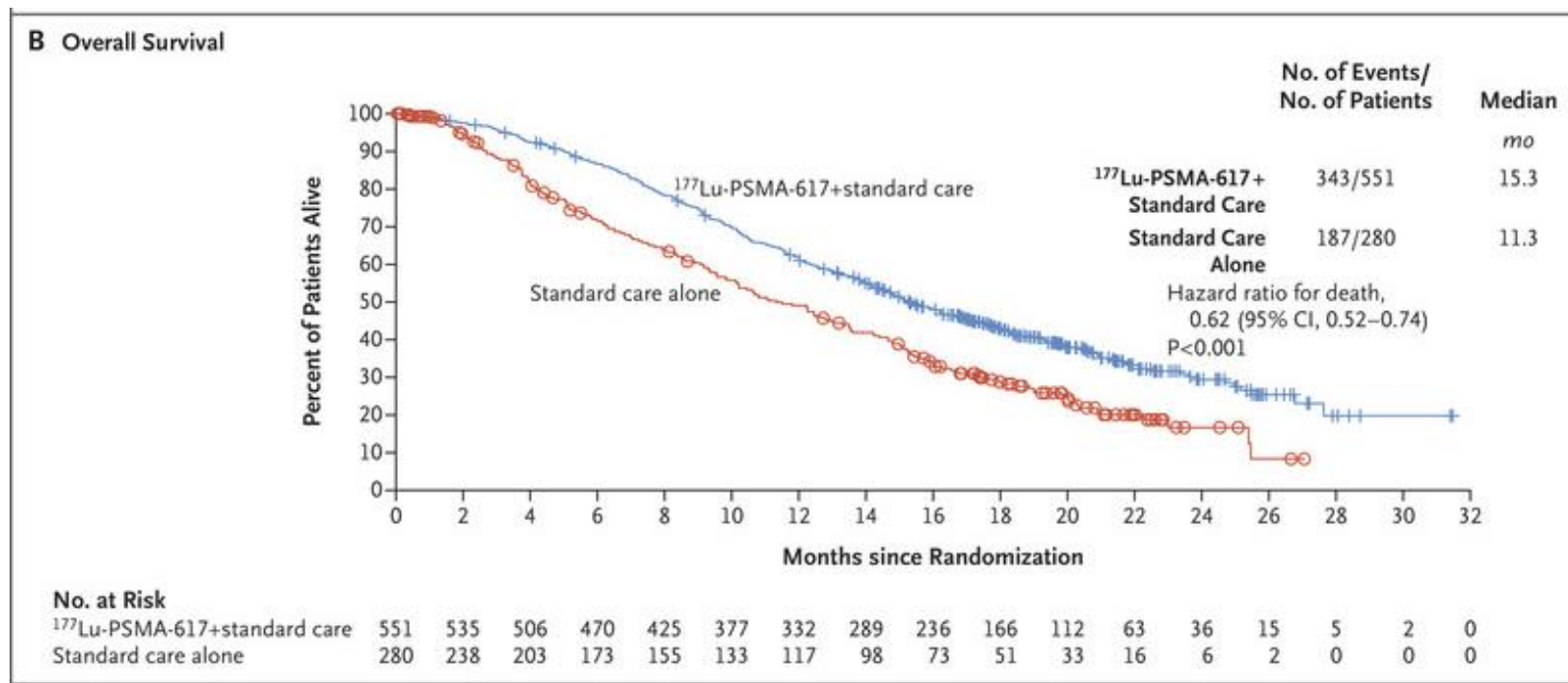


Sartor et al (N Engl J Med 2021;385:1091-103) – Studio VISION

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Table 2. Adverse Events.*

Event	¹⁷⁷ Lu-PSMA-617 plus Standard Care (N=529)		Standard Care Alone (N=205)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	<i>number of patients (percent)</i>			
Any adverse event	519 (98.1)	279 (52.7)	170 (82.9)	78 (38.0)
Adverse event that occurred in >12% of patients				
Fatigue	228 (43.1)	31 (5.9)	47 (22.9)	3 (1.5)
Dry mouth	205 (38.8)	0	1 (0.5)	0
Nausea	187 (35.3)	7 (1.3)	34 (16.6)	1 (0.5)
Anemia	168 (31.8)	68 (12.9)	27 (13.2)	10 (4.9)
Back pain	124 (23.4)	17 (3.2)	30 (14.6)	7 (3.4)
Arthralgia	118 (22.3)	6 (1.1)	26 (12.7)	1 (0.5)
Decreased appetite	112 (21.2)	10 (1.9)	30 (14.6)	1 (0.5)
Constipation	107 (20.2)	6 (1.1)	23 (11.2)	1 (0.5)
Diarrhea	100 (18.9)	4 (0.8)	6 (2.9)	1 (0.5)
Vomiting	100 (18.9)	5 (0.9)	13 (6.3)	1 (0.5)
Thrombocytopenia	91 (17.2)	42 (7.9)	9 (4.4)	2 (1.0)
Lymphopenia	75 (14.2)	41 (7.8)	8 (3.9)	1 (0.5)
Leukopenia	66 (12.5)	13 (2.5)	4 (2.0)	1 (0.5)
Adverse event that led to reduction in ¹⁷⁷ Lu-PSMA-617 dose	30 (5.7)	10 (1.9)	NA	NA
Adverse event that led to interruption of ¹⁷⁷ Lu-PSMA-617†	85 (16.1)	42 (7.9)	NA	NA
Adverse event that led to discontinuation of ¹⁷⁷ Lu-PSMA-617†	63 (11.9)	37 (7.0)	NA	NA
Adverse event that led to death‡	19 (3.6)	19 (3.6)	6 (2.9)	6 (2.9)

Safety: The incidence adverse events of grade 3 or above was higher with ¹⁷⁷Lu-PSMA-617 than with standard care alone, but most adverse events with ¹⁷⁷Lu-PSMA-617 were grade 1 or 2.

Sartor et al (N Engl J Med 2021;385:1091-103)
– Studio VISION

^{177}Lu -PSMA - Studio dosimetrico



Discovery NM/CT 670 scanner

Dual-head gamma camera with 3/8"-thick NaI(Tl) crystals

Collimators:

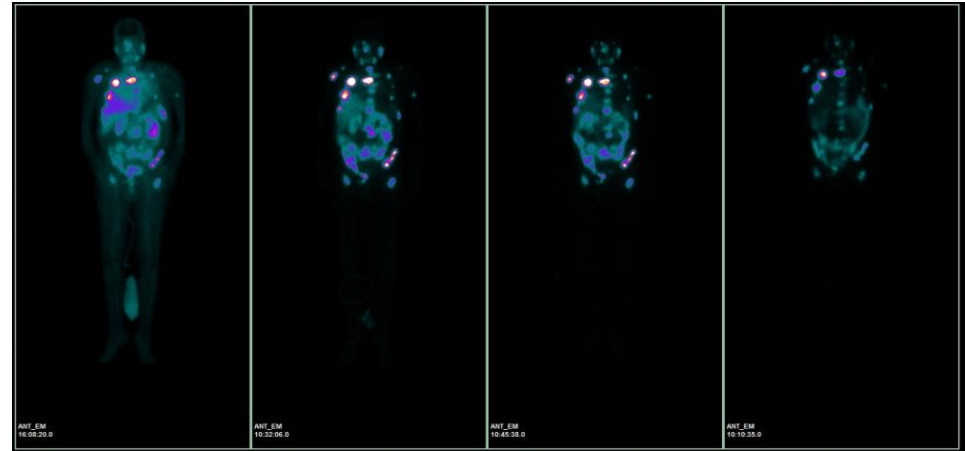
- medium-energy high-resolution (MEHR)
- high-energy high-resolution (LEHR)

Energy windows acquisition with ^{177}Lu -PSMA:

- Dominant photopeak energy (208 keV, 10% width)
- Low scatter (175 keV, -5% / +6% width)
- High scatter (238 keV, -3% / +5% width)

- ✓ 20 ^{177}Lu -PSMA (Phase II trial)
- ✓ Immagini whole body post infusione a 1, 16-24, 36-48 e 120h

- Sarnelli et al Molecules 2019**
- Paganelli et al EJNMI 2020**

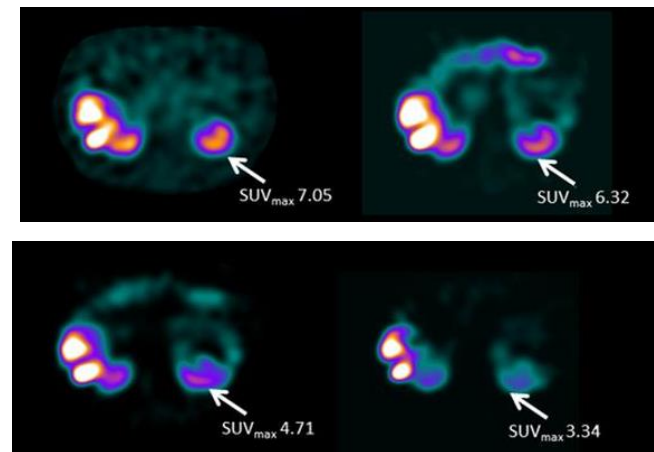


Giorno 1
(30min-1h)

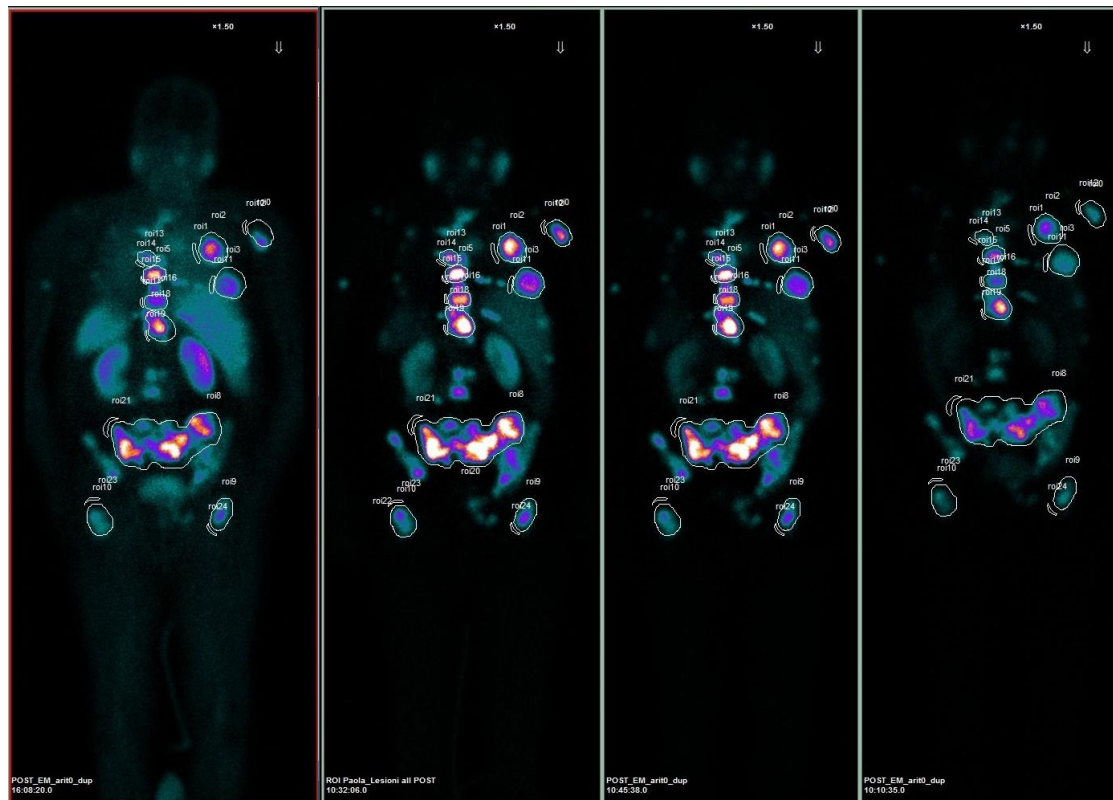
2
(16-24h)

3
(36-48h)

5
(120h)



WB posteriore – varie captazioni scheletriche



Giorno 1
1h post infusione

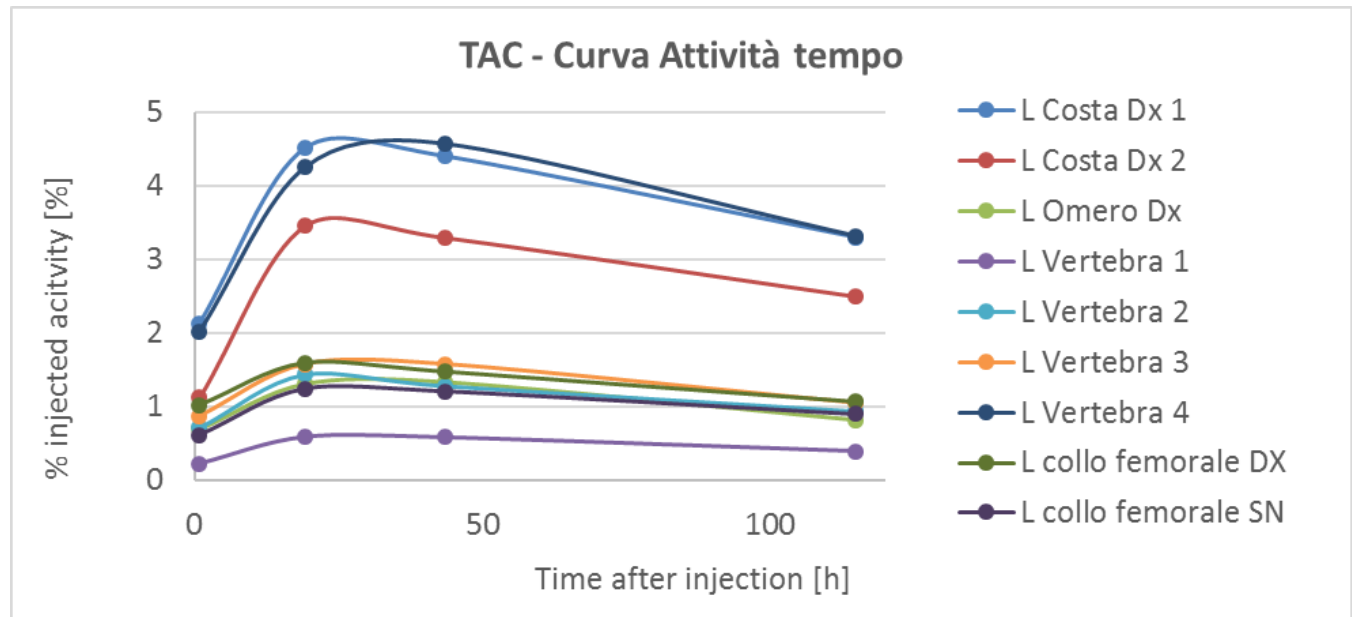
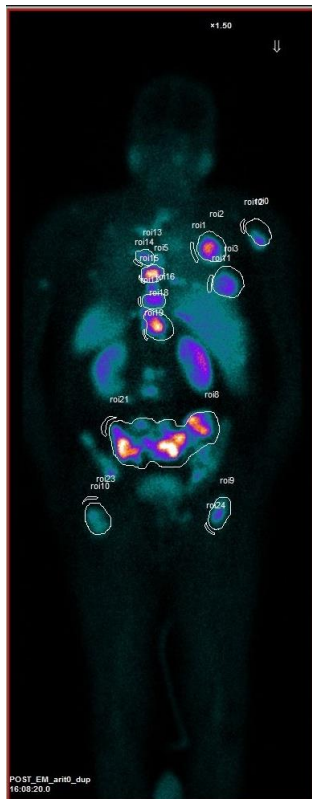
Giorno 2
19 h

Giorno 3
44 h

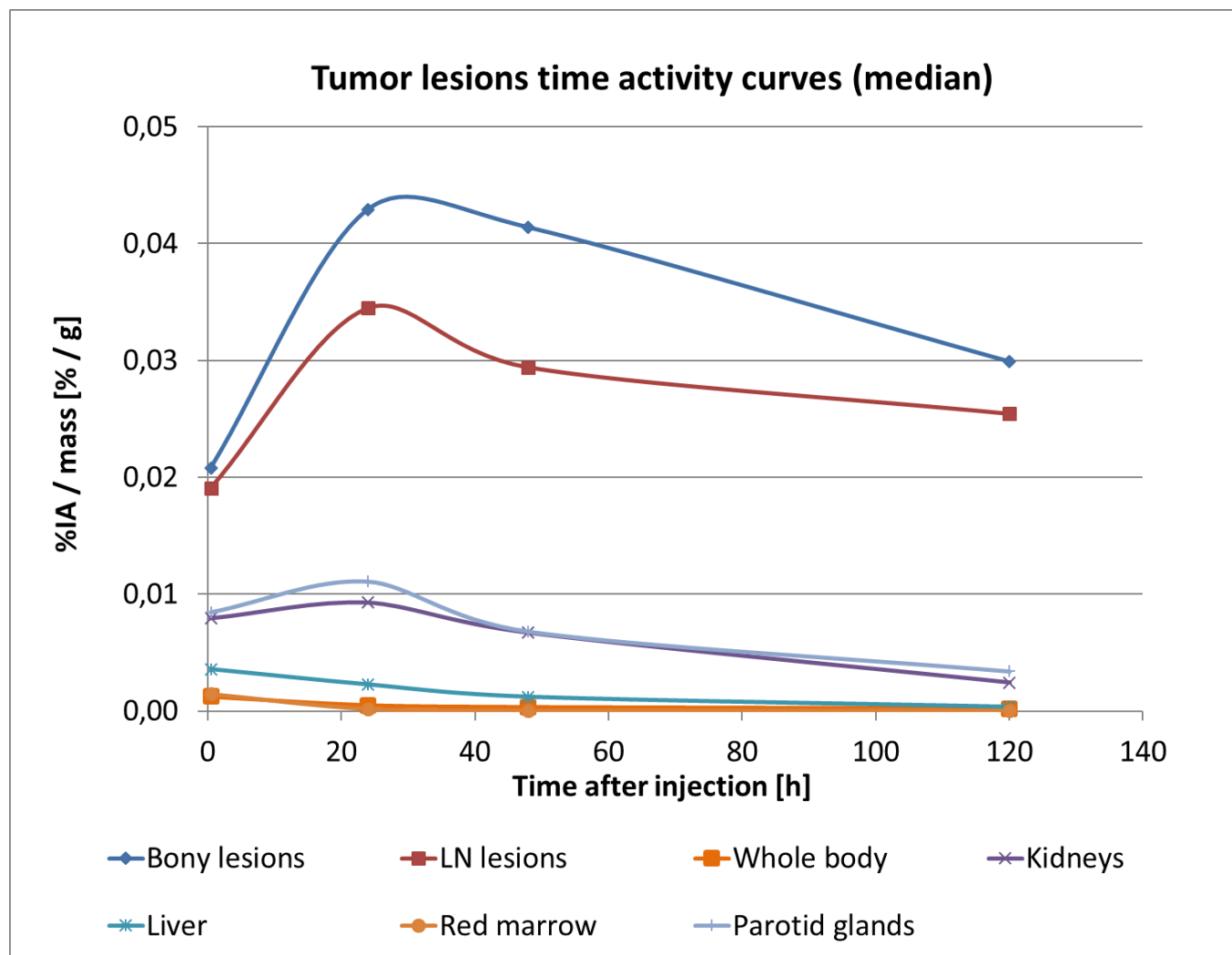
Giorno 5
115 h

Paziente di 65 anni; ^{177}Lu -PSMA; Ciclo 1: 150 mCi (5,5 GBq); 4 whole body planari post infusione

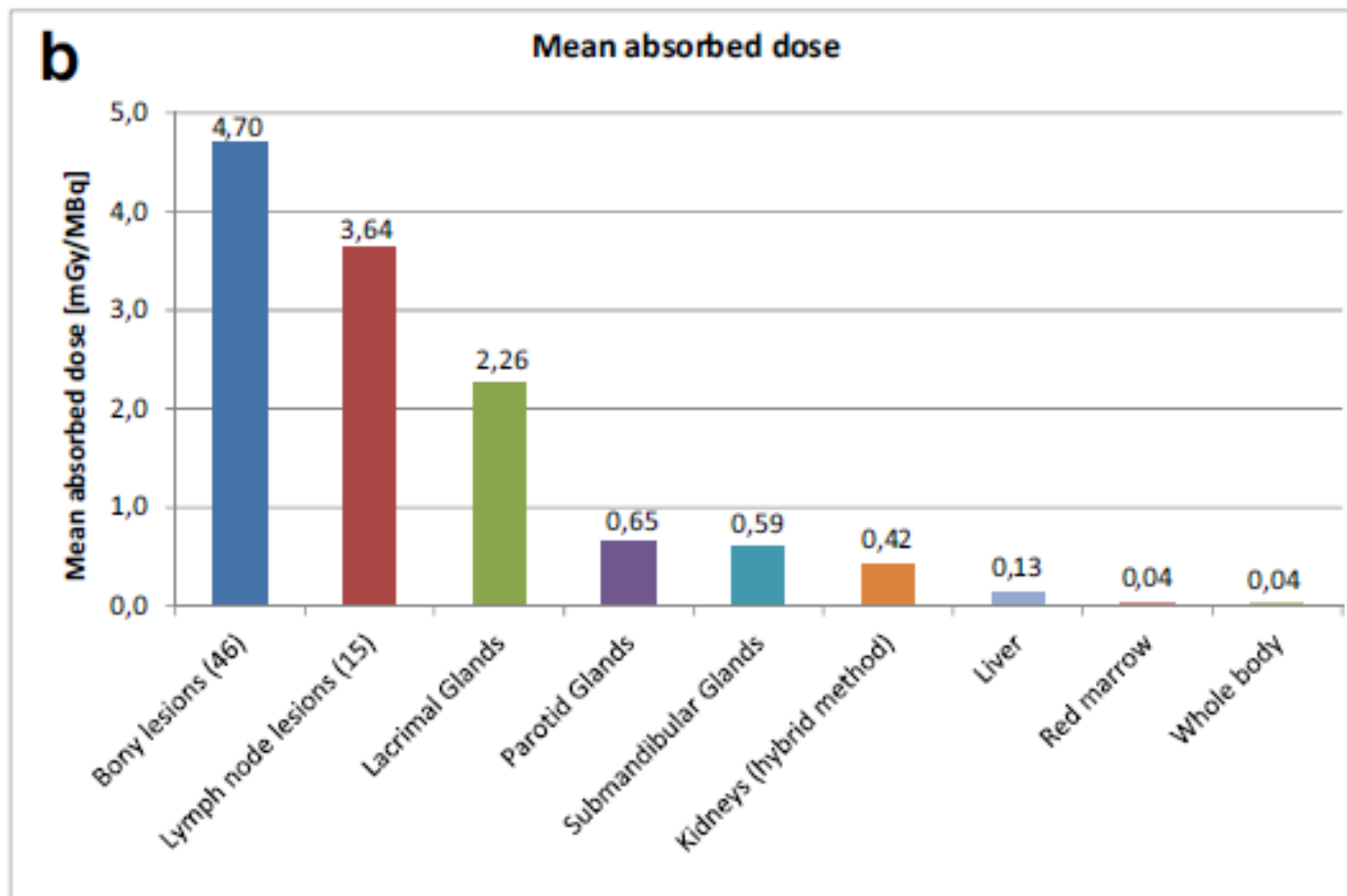
WB posteriore – varie captazioni scheletriche



Paziente di 65 anni; ^{177}Lu -PSMA; Ciclo 1: 150 mCi (5,5 GBq); 4 whole body planari post infusione



Paganelli et al (EJNMMI 2020, 47(13):3008–3017)



Studio dosimetrico

- Formalismo MIRD (ph + sfera omogenea acqua)
- Volume: ^{68}Ga PET/CT pre terapia
- Dose media

Paganelli et al (EJNMMI 2020, 47(13):3008–3017)

Table 3 Dosimetry results for tumor lesions

Patient no.	Injected activity (GBq)	Dosimetry performed at 1st or 2nd cycle	Lesion location (no.)	Mass (g)			Mean absorbed dose (mGy/MBq)		
				Median	Minimum	Maximum	Median	Minimum	Maximum
1	5.5	1st	Bone (10)	39.0	13.8	382.6	6.19	1.55	9.09
2	4.4	1st	Bone (1)	104.0	–	–	12.00	–	–
			Lymph node (3)	23.4	18.5	36.1	3.64	2.44	5.90
3	4.4	1st	Lymph node (3)	2.6	2.1	22.7	2.64	2.10	8.09
4	4.4	1st	Bone (1)	12.8	–	–	1.27	–	–
			Lymph node (1)	3.8	–	–	0.25	–	–
5	4.4	1st	Bone (14)	17.0	2.3	574.4	4.73	1.71	55.86
6	4.4	2nd	Bone (1)	6.0	–	–	1.57	–	–
			Lymph node (3)	6.9	6.9	8.1	4.22	1.59	13.24
7	5.5	1st	Bone (4)	27.9	12.9	39.5	5.58	3.62	7.51
			Lymph node (2)	51.8	46.9	56.7	10.36	5.62	15.10
8	4.4	1st	Bone (3)	95.5	89.8	184.8	2.63	1.24	4.81
9	5.5	2nd	Bone (2)	7.6	4.8	10.4	3.50	0.74	6.26
10	5.5	1st	Bone (3)	3.7	3.4	5.2	1.40	1.26	2.80
			Lymph node (2)	3.6	2.6	4.6	1.80	1.30	2.30
11	5.5	2nd	Bone (3)	21.8	9.8	25.7	2.29	1.01	3.17
			Lymph node (1)	2.0	–	–	9.18	–	–
12	5.5	2nd	Bone (1)	91.4	–	–	1.34	–	–
13	4.4	1st	Bone (3)	6.7	3.2	15.5	4.83	0.97	9.48
All lesions				17.8	2.0	38.5	4.27	0.25	9.18
Bone				21.8	2.3	574.5	4.70	0.74	55.86
Lymph node				6.9	2.0	56.7	3.64	0.25	15.10

4,4 – 5,5 GBq →

21	4	245
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 Gy

7,4 GBq →

35	5	413
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 Gy

Paganelli et al (EJNMMI 2020, 47(13):3008–3017)

Patient no.	Injected activity (GBq)	Dosimetry performed at 1st or 2nd cycle	Mean absorbed dose (mGy/MBq)						
			Parotid glands	Submandibular glands	Lacrimal glands	Kidneys	Liver	Red marrow	Whole body
1	5.5	1st	1.21	0.67	0.86	0.53	0.11	–	0.113
2	4.4	1st	2.63	1.20	3.54	0.21	0.10	0.044	0.035
3	4.4	1st	0.79	0.32	2.99	0.56	0.15	–	0.044
4	4.4	1st	0.41	0.59	0.82	0.15	0.05	0.023	0.018
5	4.4	1st	0.65	0.51	2.83	0.14	0.05	0.067	0.088
6	4.4	2nd	2.46	1.51	2.26	0.81	0.24	–	0.068
7	5.5	1st	0.33	0.23	2.95	0.31	0.53	0.033	0.043
8	4.4	1st	1.33	0.77	0.65	0.32	0.06	0.028	0.135
9	5.5	2nd	0.37	0.69	3.44	0.48	0.13	0.036	0.027
10	5.5	1st	1.93	0.59	0.62	0.60	0.12	–	0.028
11	5.5	2nd	0.48	0.57	0.48	0.37	0.14	0.061	0.038
12	5.5	2nd	0.41	0.75	3.59	0.49	0.19	–	0.033
13	4.4	1st	0.49	0.26	1.69	0.42	0.42	–	0.025
Median			0.65	0.59	2.26	0.42	0.13	0.036	0.038
Min			0.33	0.23	0.48	0.14	0.05	0.023	0.018
Max			2.63	1.51	3.59	0.81	0.53	0.067	0.135
5,5 GBq →			3,6	3,2	12,4	2,3	0,7	0,19	0,21
X 4 cicli			14	13	50	9	3	0,8	0,8
7,4 GBq →			4,8	4,4	16,7	3,1	0,9	0,27	0,28
X 4 cicli			19	18	67	12	3,6	1,1	1,1

Paganelli et al (EJNMMI 2020, 47(13):3008–3017)

74 pts

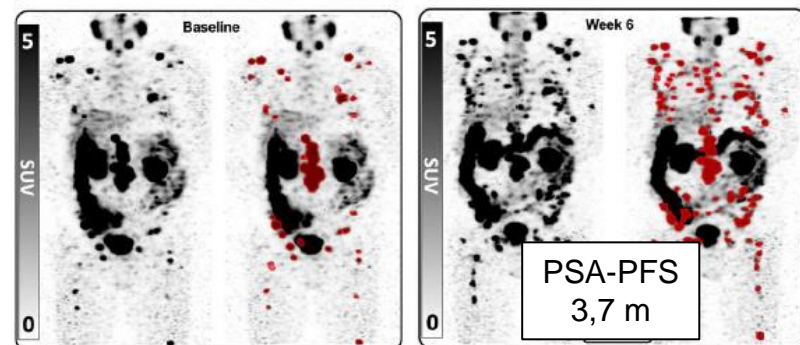
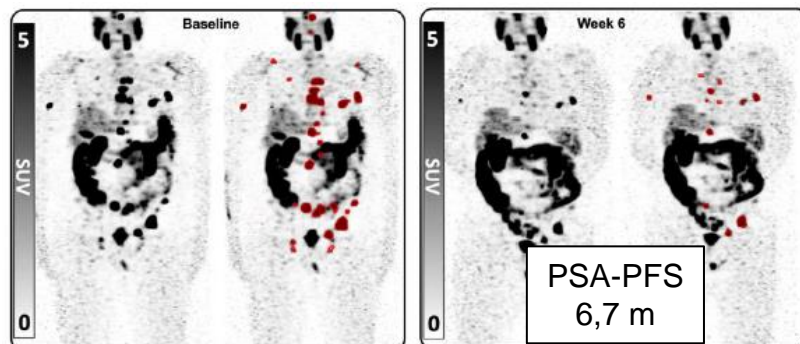
8 GBq /cycle ^{177}Lu -PSMA I&T – 3 cycles (range: 2-5)

SPECT at cycle 1 and 2



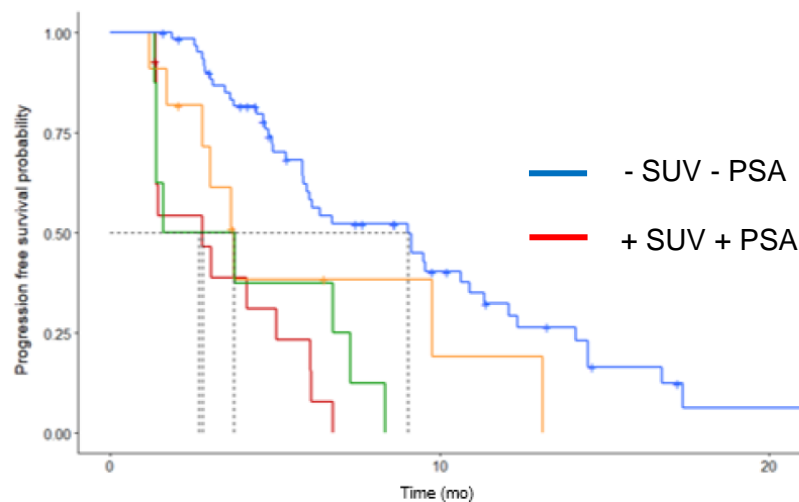
Cycle 1, Baseline

Cycle 2, 6 weeks



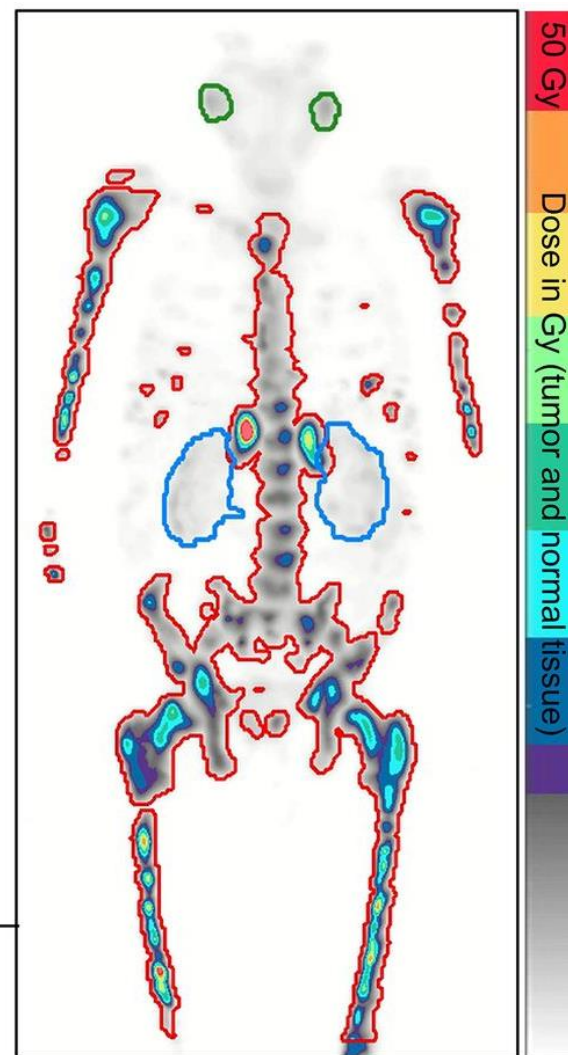
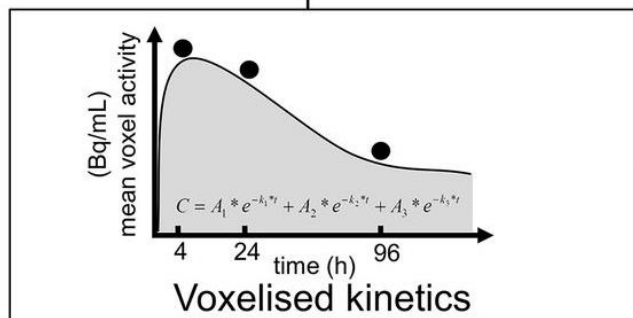
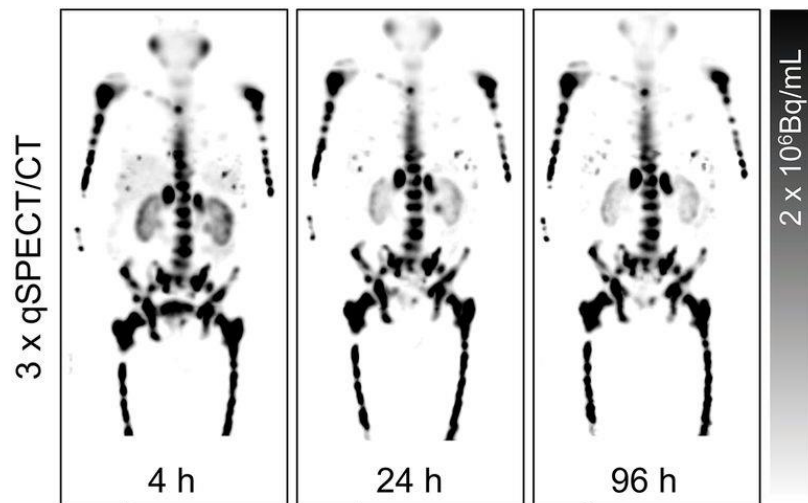
	PSA-PFS	OS
Δ SPECT-TTV	2,5 (1,5-4,2) [$<0,01$]	1,2 (0,6-2,7) [0,6]
Δ SPECT SUV_{mean}	2,1 (1,2-3,8) [0,01]	1,7 (0,7-4,0) [0,2]
Δ SPECT SUV_{max}	1,8 (1,0-3,1) [0,04]	1,3 (0,6-2,8) [0,6]

HR (95% CI) [p]



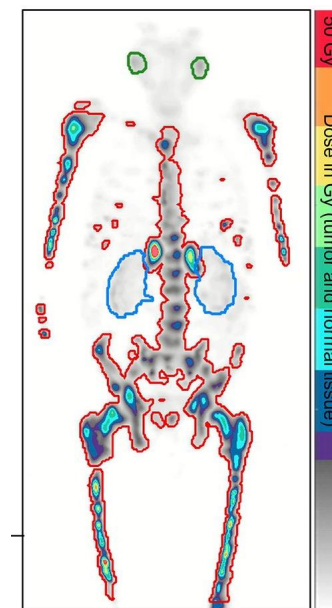
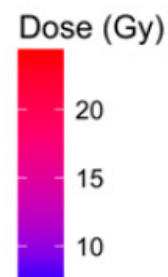
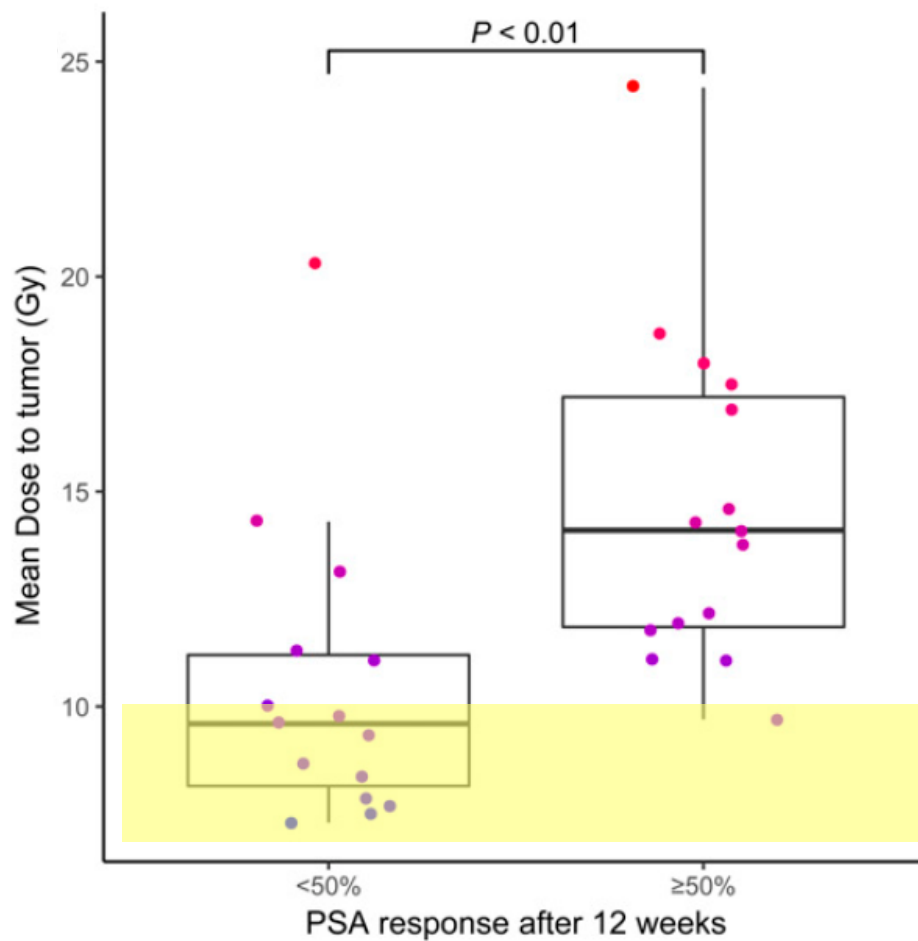
Jhon et al (JNM 2022, Sept 8) – EANM Barcellona 2022

30 pts
 8 GBq /cycle ^{177}Lu -PSMA-617 – 4 cycles
 SPECT/CT dosimetry (2 or 3 bed position)



Soglia 5 Gy per il volume totale di malattia

Violet et al (JNM 2019, 60:517-523)



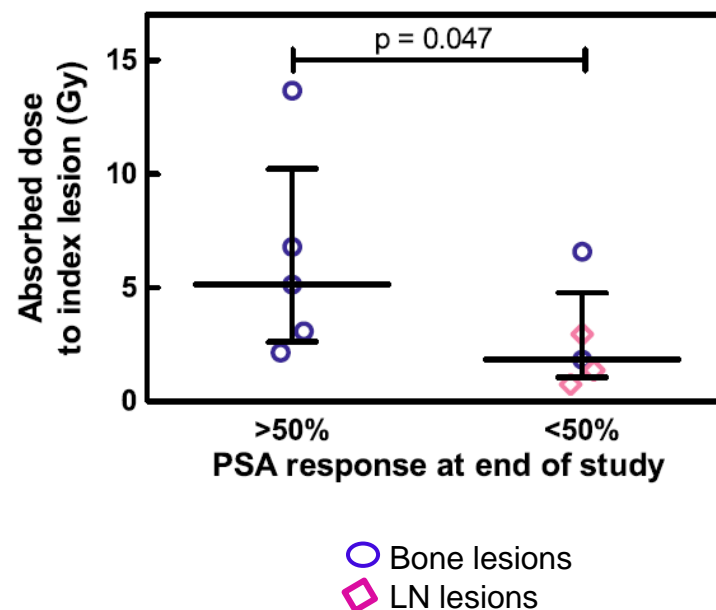
<10Gy
10 non-responders
1 responder

Violet et al (JNM 2019, 60:517-523)

177Lu-PSMA-617 to low-volume hormone-sensitive metastatic PC (mHSPC) pts
 10 pts
 C1: 3 GBq – C2: 3 to 6 GBq

Table 3 Absorbed dose in organs at risk (Gy/GBq)

	Salivary glands	Kidneys	Liver	Bone marrow
Mean + SD	0.39 ± 0.17	0.49 ± 0.11	0.09 ± 0.01	0.017 ± 0.008
Median	0.38	0.49	0.09	0.018
Range	0.14–0.66	0.34–0.66	0.07–0.12	0.013–0.023



Peters et al (JNM 2022, 49:460-469)

Work in progress:

- Implementazione clinica della dosimetria routinaria
- Standardizzazione
- BED (Biological Effective Dose) e EQD2 (Dose equivalente in 2Gy/fr)
- Dose minima, media?
- Modulazione dell'attività sulla base della dosimetria?
- Barre di errore?

Nodi da sciogliere:

- Rimborsi dosimetria
- Dosimetria accurata vs ricovero
- Anticipo terapia recettoriale (trail clinici on going NCT04689828, NCT04720157, NCT03828838)

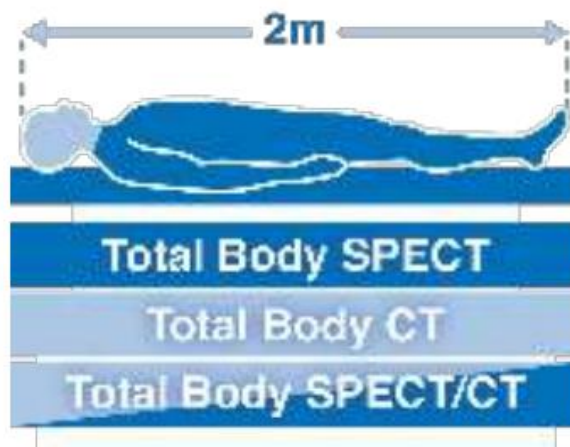


SPECTRUM
DYNAMICS MEDICAL
VERITON-CT
SPECT/CT



- Acquisizione simultanea su 360°
- Minima distanza paziente-testata
- 32 Axial FOV
- Rivelatori CZT
- Risoluzione spaziale maggiore (4.8 mm vs 2.5*)
- CT 16/64 slice
- FOV CT/NM: 80 cm
- Software analisi e refertazione

StartGuide Ge



Whole-body bone scintigraphy in a 14 y/o patient

Anterior Anger
planar view



Imm planare
15 min

Anterior MIP
CZT-SPECT view



Imm SPECT/CT
18 min

Summed coronal
CZT-SPECT view



* Imbert et al, JNM 2019; 60(1):

Take home message

- Possiamo vedere (carico di malattia) e misurare (dosimetria)
- Questo ci dà **informazioni** predittive dell'outcome del trattamento
- Un approccio teragnostico **aiuta nella decisione clinica del trattamento**, permettendo di andare sempre più verso una **medicina personalizzata e di precisione**
- Data la nuova tecnologia (e le richieste di legge D.Lgs. 101/2020) è **opportuno** pensare a studi dosimetrici, ai singoli pazienti o gruppi di pazienti
- Necessario trovare **risorse adeguate** (strumentazione, personale, rimborso, formazione, studi multi-centrici....)

Grazie

per l'attenzione

ISTITUT
ROMAGNOLO
PER LO STUDIO
DEI TUMORI
DINO AMADORI

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori"
Istituto di Ricovero e Cura a Carattere Scientifico

*...e grazie a tutti i colleghi che hanno collaborato in vario modo!!
Anna Sarnelli, Giovanni Pagannelli, Antonino Romeo, Ugo De Giorgi,e tanti altri*





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