

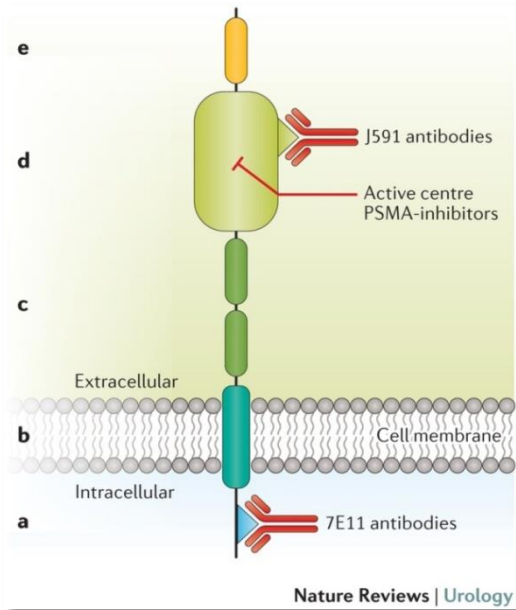
VII SESSIONE
I NUOVI FARMACI OSTEO-ONCOLOGICI NELLE NEOPLASIE BIG KILLERS
Moderatori: Giuseppe Tonini, Toni Ibrahim, Giampaolo Tortora, Alfredo Berruti



Terapia radiometabolica:
farmaci target per la terapia delle
metastasi ossee.
Posizionamento nel paziente con
carcinoma della prostata

Dr. Stefano Severi
IRCCS-IRST Meldola ITALY

PSMA: Prostate Specific Membrane Antigen



Glicoprotein highly
expressed in prostatic cancer,
as specific target
CARBOSSIPEPTIDASI II (GCP II)

> J Org Chem. 2019 Jun 7;84(11):7501-7508. doi: 10.1021/acs.joc.9b00832. Epub 2019 May 15.

HBED-NN: A Bifunctional Chelator for Constructing Radiopharmaceuticals

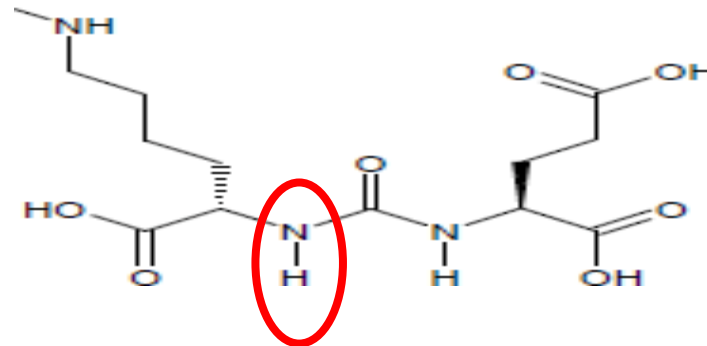
Ata Makarem¹, Karel D Klika², German Litau¹, Yvonne Remde¹, Klaus Kopka^{1 3}

SPECIFIC PSMA INIBITOR

Lysine- urea-glutamate

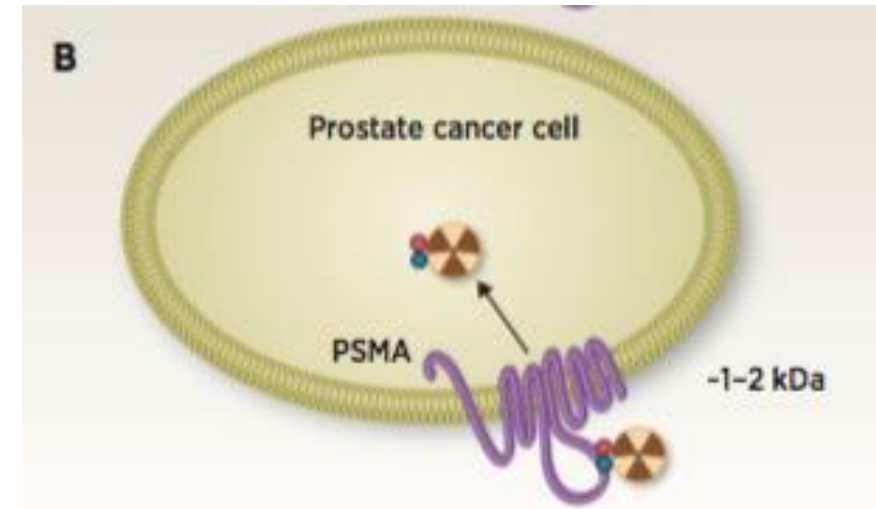
Lys-NH-CO-NH-Glu:

ureid-based inhibitor of GCP II



PSMA and PCa

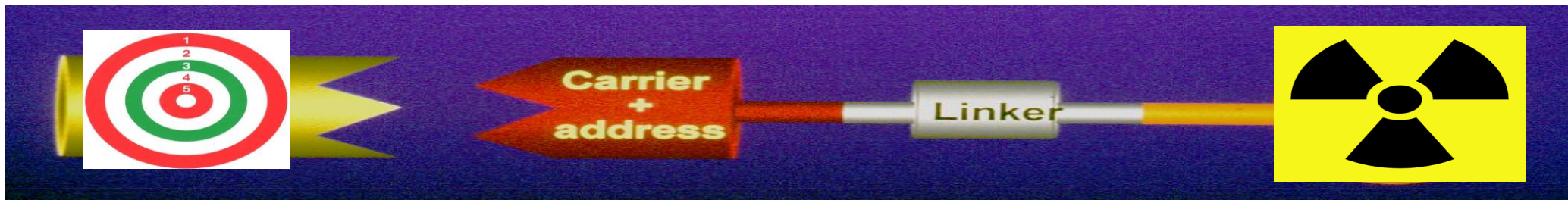
- **PSMA overexpressed on CRPC cells membrane:**
 - Highly **specific target**
- **PSMA increased expression in:**
 - High Gleason Score
 - CRPC (revCRPC < CRPC < CRPC_{AA})
 - On Testosterone withdrawal
- **PSMA internalisation upon binding with inhibitors:**
 - Suitable for **therapy**



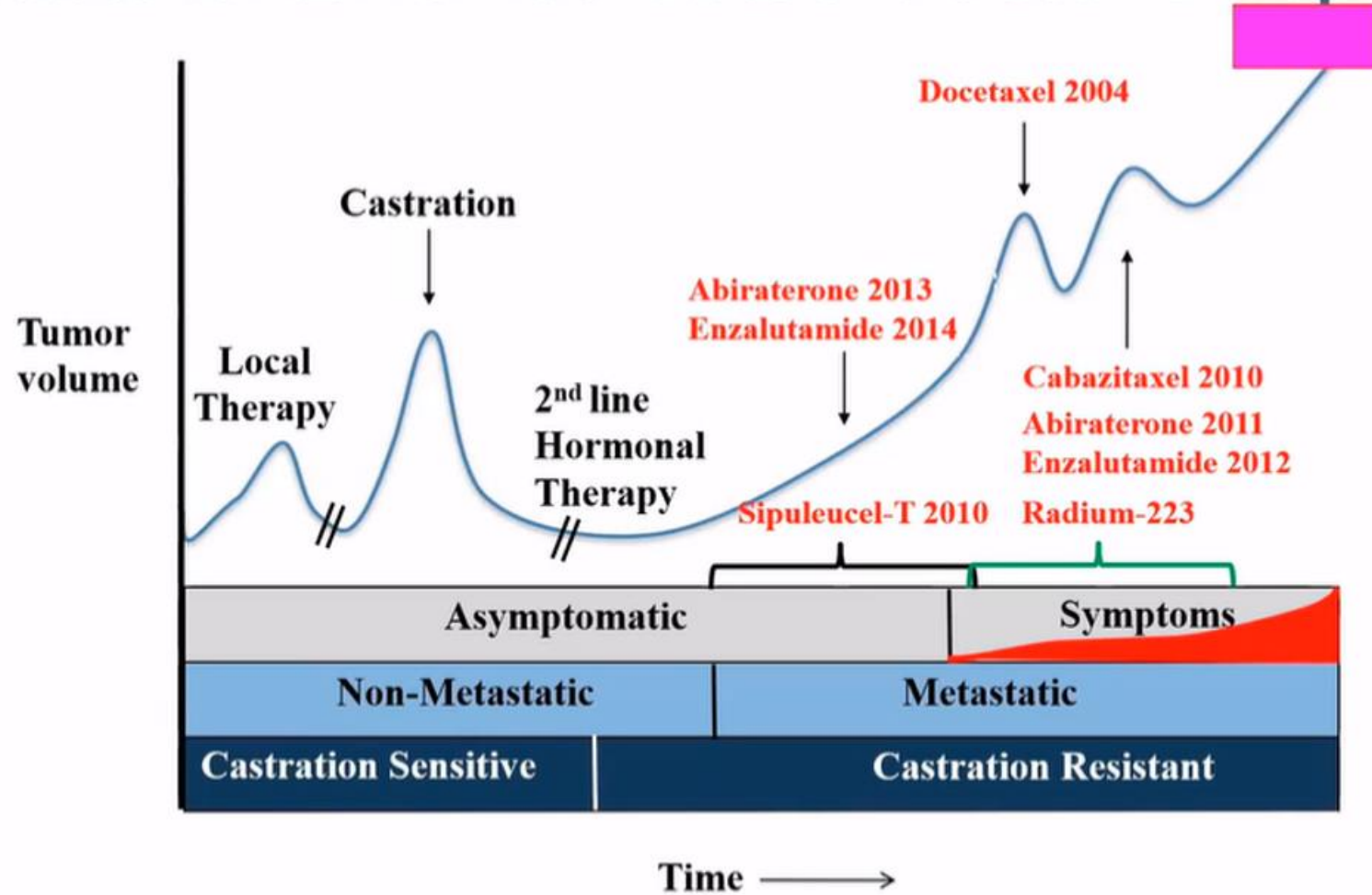
The therapeutic radiopharmaceutical is obtained by marking the ^{177}Lu radionuclide with the urea inhibitor of PSMA through the chelating agent

The ^{177}Lu is physically characterized by:

- **Half life 6.7 days;**
- **Emission of β - particles with energy of 497 keV (78.6%), 384 keV (9.1%) and 176 keV (12.2%) with tissue penetration power of 1-2 mm;**
- **Low energy γ -ray emission of 208 and 113 keV with an abundance of 10% and 6% respectively, which allow to acquire a scintigraphic images**



Prostate cancer: clinical state and treatment options



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Radiometabolic Therapy (RMT) with ^{177}Lu PSMA 617 in advanced castration resistant prostate cancer (CRPC): efficacy and toxicity evaluation

EU trial n.2016-002732-32

Protocol Code:IRST185,03

-Primary: DCR and toxicity

-Secondary: Late toxicity, PFS, OS, Biochemical response, dosimetry

Study Design

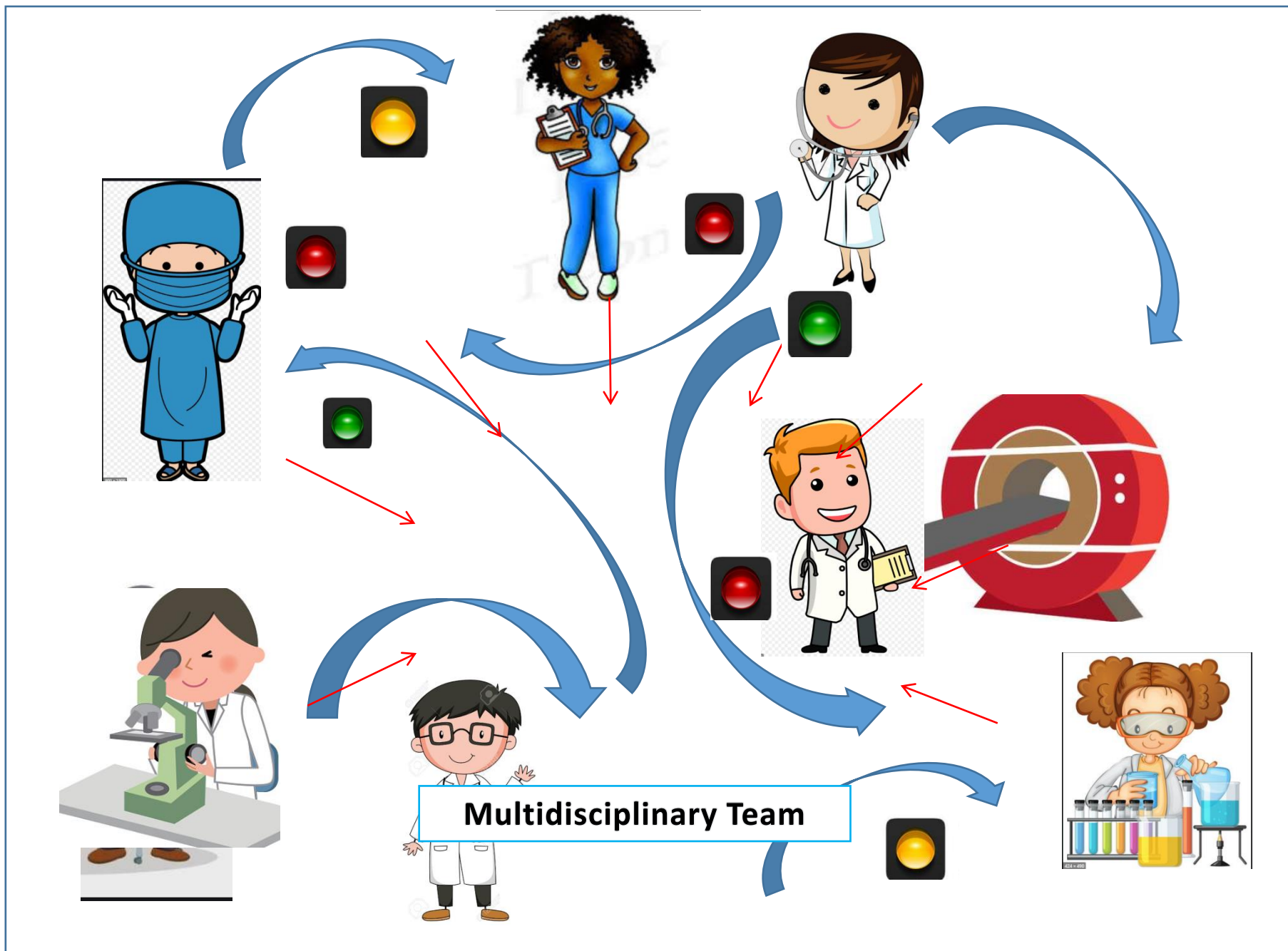
Characteristics	Treatment	Option
age ≥ 75 Or Docetaxel	^{177}Lu -PSMA 3.7-4.2 GBq 8-12 wk x 4 cycles	+ 1-2 additional cycles
age < 75 No Docetaxel	^{177}Lu -PSMA 5.5 GBq 8-12 wk x 4 cycles	+ 1-2 additional cycles



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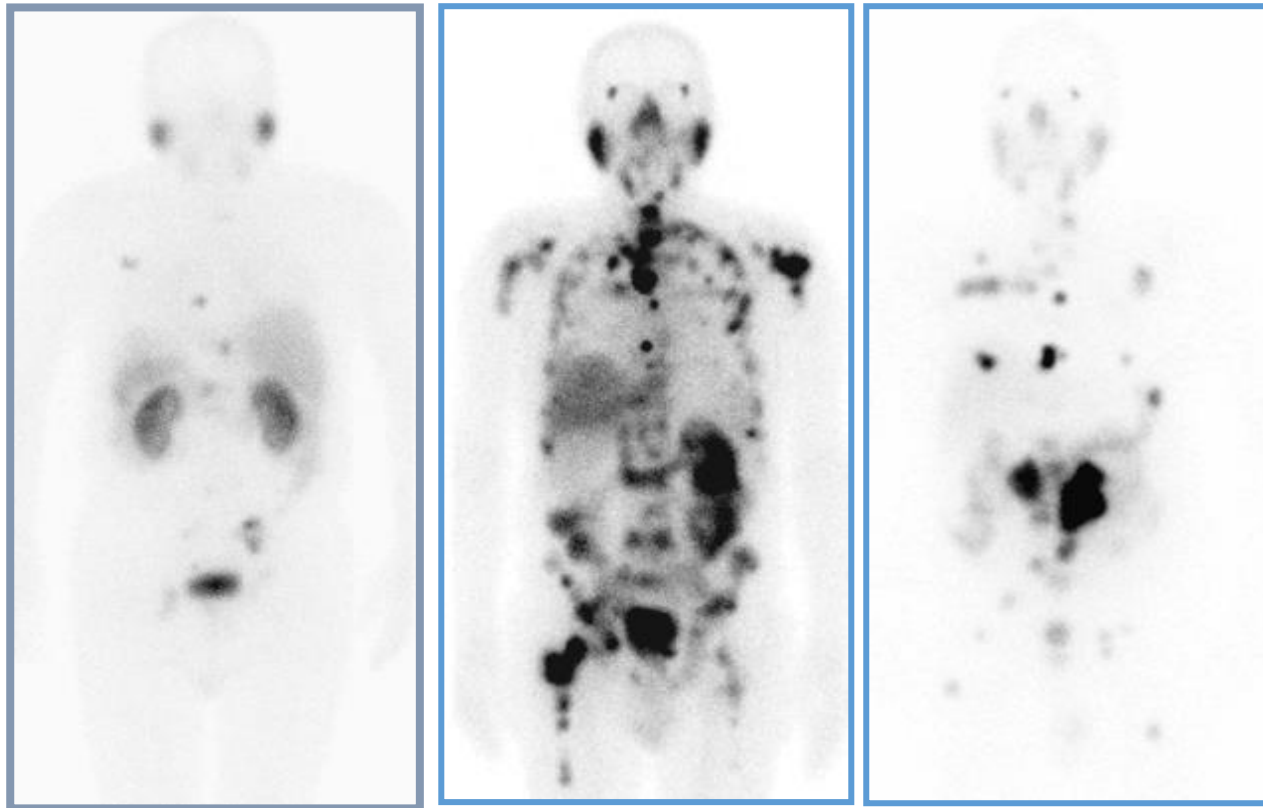
Prognostic Factors

LU-PSMA POST RLT CAPTATION SCORE+

1 = parotid

2 > parotid

3 > kidney



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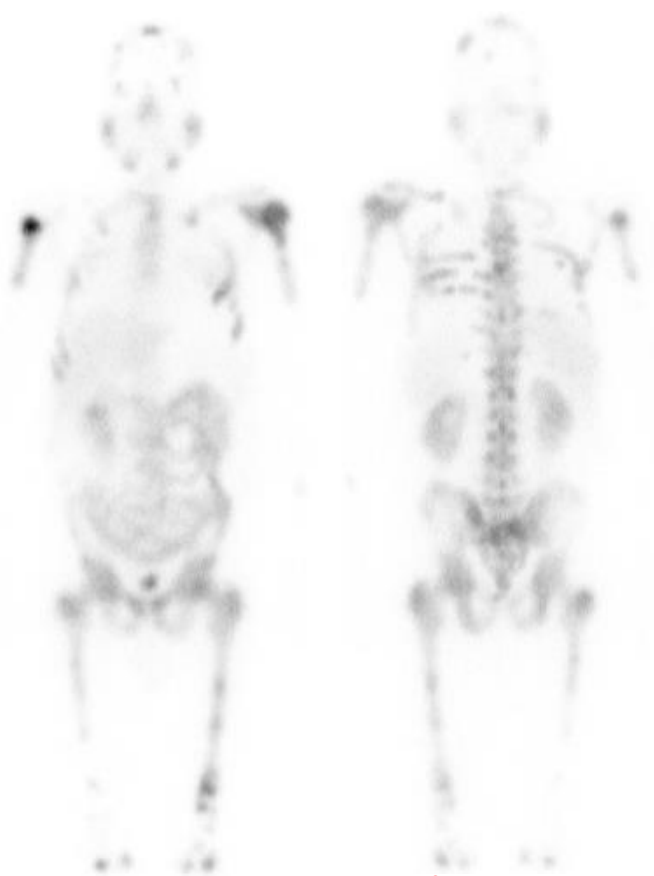
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M.M. 27/05/1962, mCRPC Gleason 8 (4+4). Total body after 177Lu-PSMA therapy (2° line therapy)

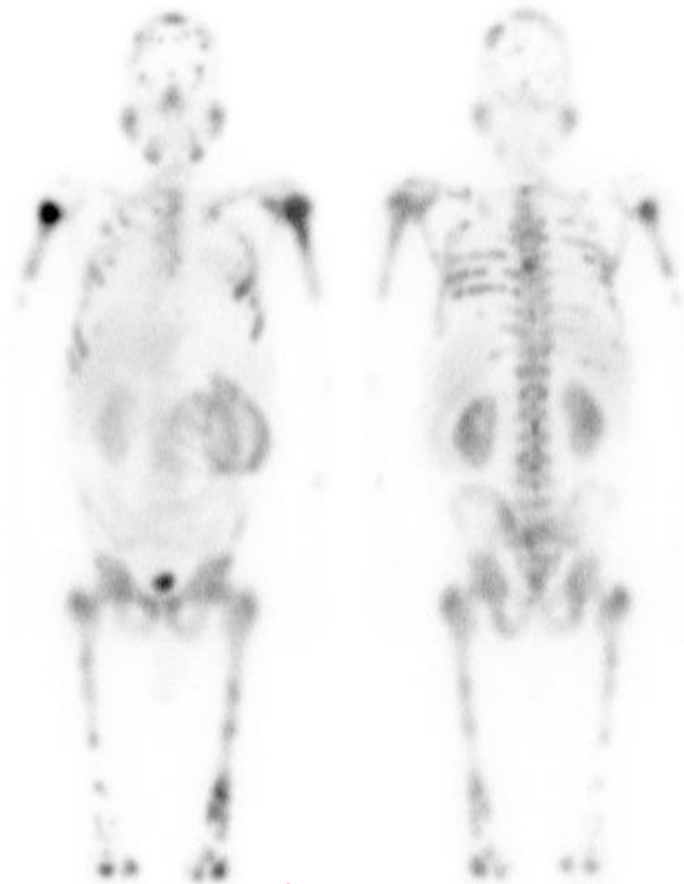


30/03/2022



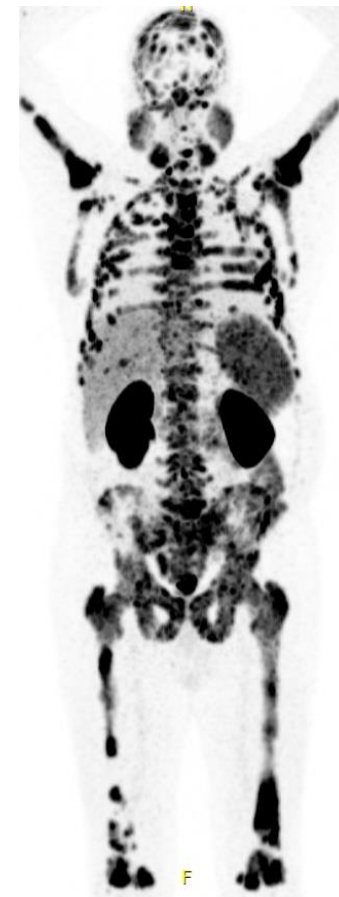
PSA Reflex (ng/ml) 1° cycle 114

27/05/2022



2° cycle 102

05/07/2022



11/08/2022



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Therapeutic efficacy, prognostic variables and clinical outcome of ^{177}Lu -PSMA-617 PRLT in progressive mCRPC following multiple lines of treatment: prognostic implications of high FDG uptake on dual tracer PET-CT vis-à-vis Gleason score in such cohort

^{1,2}SONAM SUMAN, ^{1,2}RAHUL V. PARGHANE, ^{2,3}AMIT JOSHI, ^{2,3}KUMAR PRABHASH, ^{2,4}GANESH BAKSHI,
^{2,5}SANJAY TALOLE, ^{1,2}SHARMILA BANERJEE and ^{1,2}SANDIP BASU

<https://doi.org/10.1259/bjr.20190380>

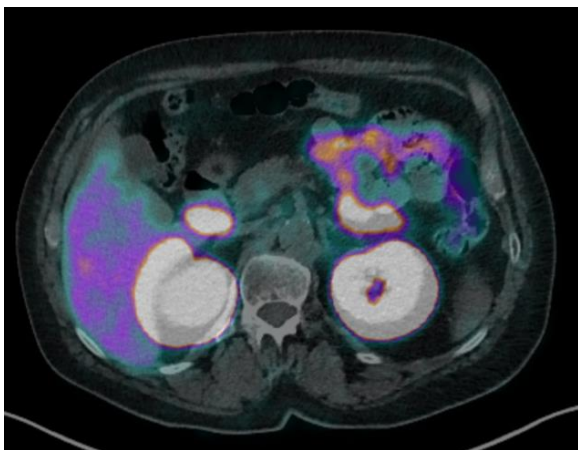
BJR

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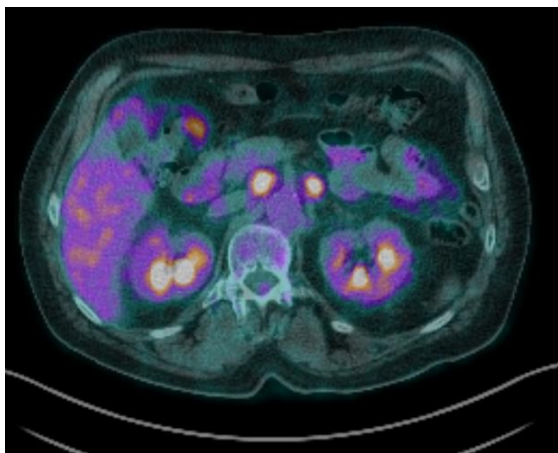
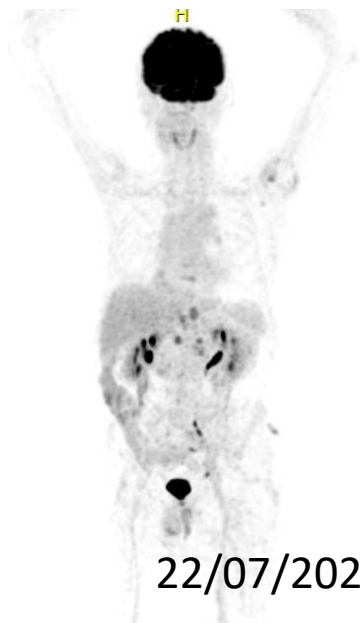
^{177}Lu -PSMA- 617 therapy was found effective in disease control with good symptomatic and biochemical responses in mCRPC patients with failed approved therapies. Even in patients with **heavily pre-treated** and advanced PD it resulted in **longer PFS and OS** and proved as a promising treatment option in this group of patients.

Patients with Gleason score 8 and above showed **higher FDG uptake** (SUVmax >7.1) which was expected; the higher FDG uptake corroborated with high Gleason score and inferior 12 month PFS. Thus, high FDG uptake with high Gleason score can be considered indicative of aggressive disease biology and would thus be a distinctive subset which may forecast an inferior outcome.

Negative **PSA doubling** correlated well with the longer PFS indirectly indicating favourable biochemical response. The ^{68}Ga -PSMA-11 avid **metastatic nodal** disease responded well with ^{177}Lu PSMA-617 PRLT as compared to the hepatic and skeletal lesions.

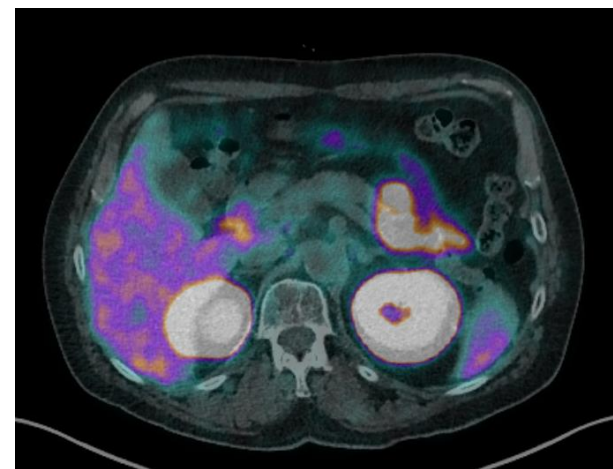


13/04/2022 68Ga PSMA pre Therapy



22/07/2022 FDG PET after 2° cycle Therapy

R.U. 05/09/1951 mCRPC GS 7 (4+3),
surgery, RT, 3° line with 177Lu-PSMA,
**Incremental PSA (baseline 12,8; 16 after
1° cycle, 17,7 after 2° cycle)**



5/8/2022 68Ga PSMA after 2° cycle Therapy

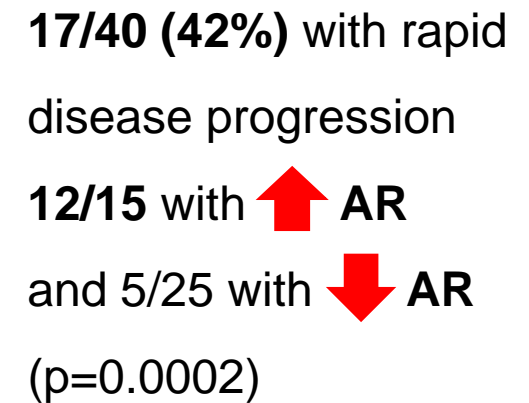


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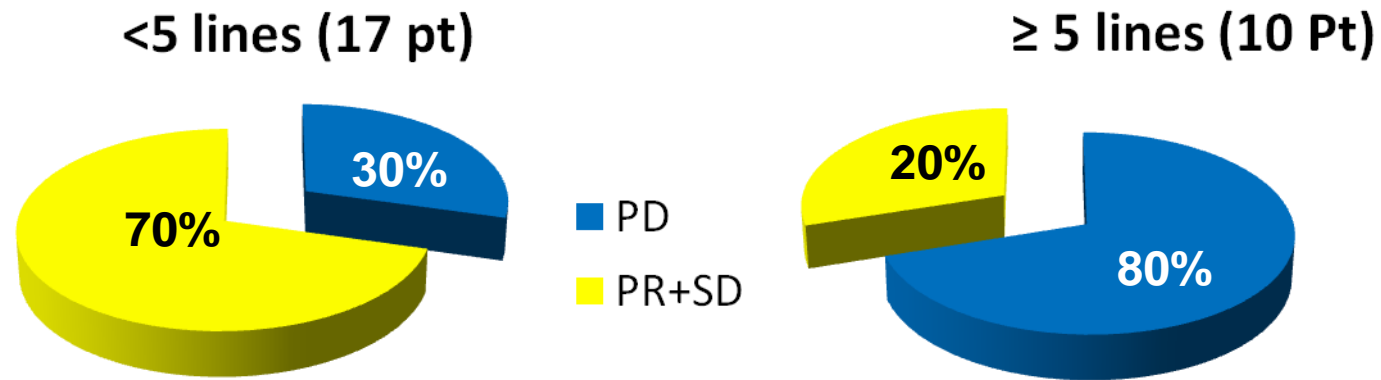
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Previous Therapy lines



Prevalence of skeletal disease

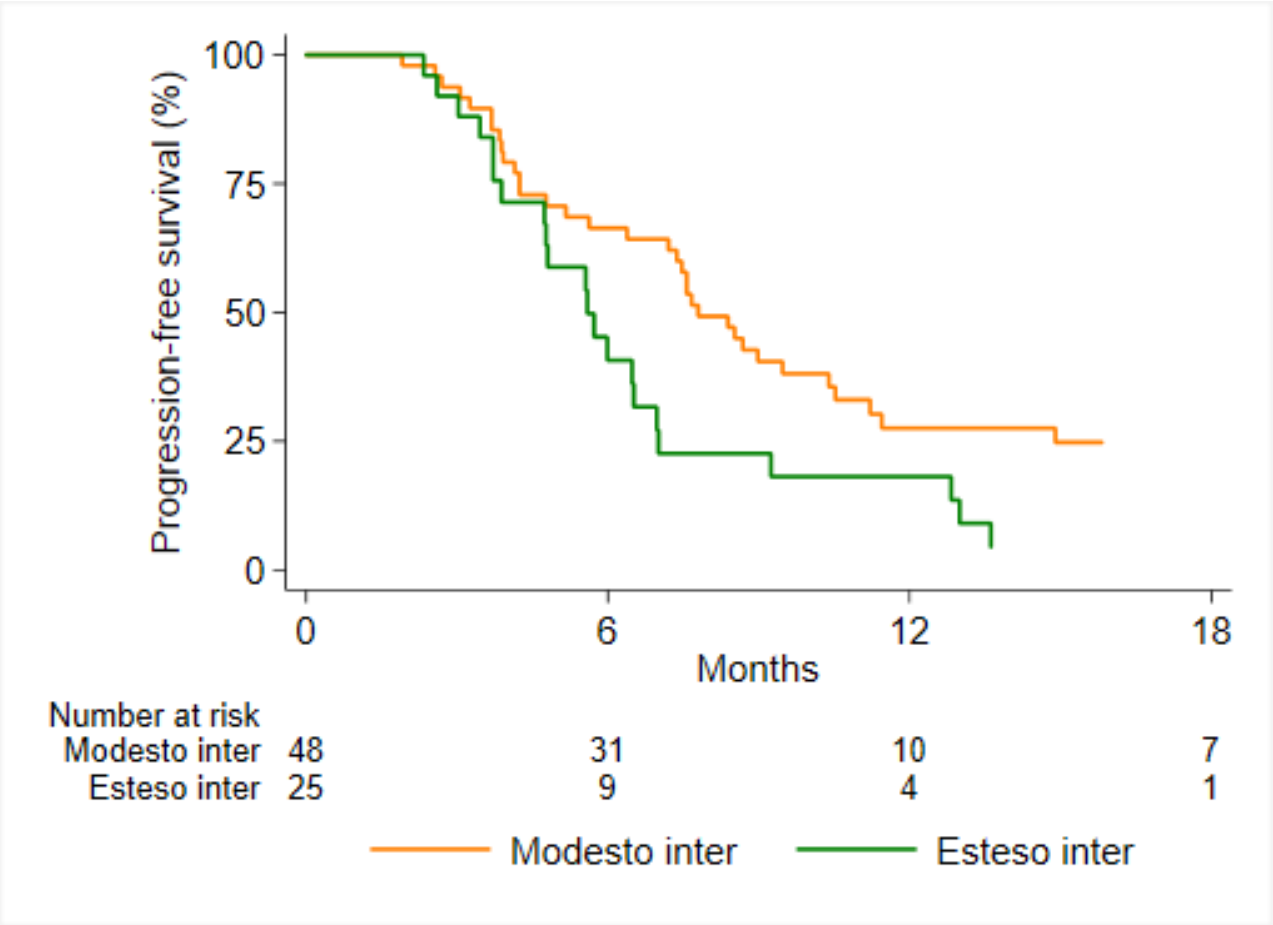
73 out of 80 patients with skeletal disease (91%) of these:

31 out of 73 patients with bone disease only (42.5%)
17 of 73 patients with moderate G1 lymph node disease (23.25%)

25 out of 73 patients with extensive G2 / 3 lymph node disease
and parenchymal disease (34.25%)



Median Progression-Free Survival

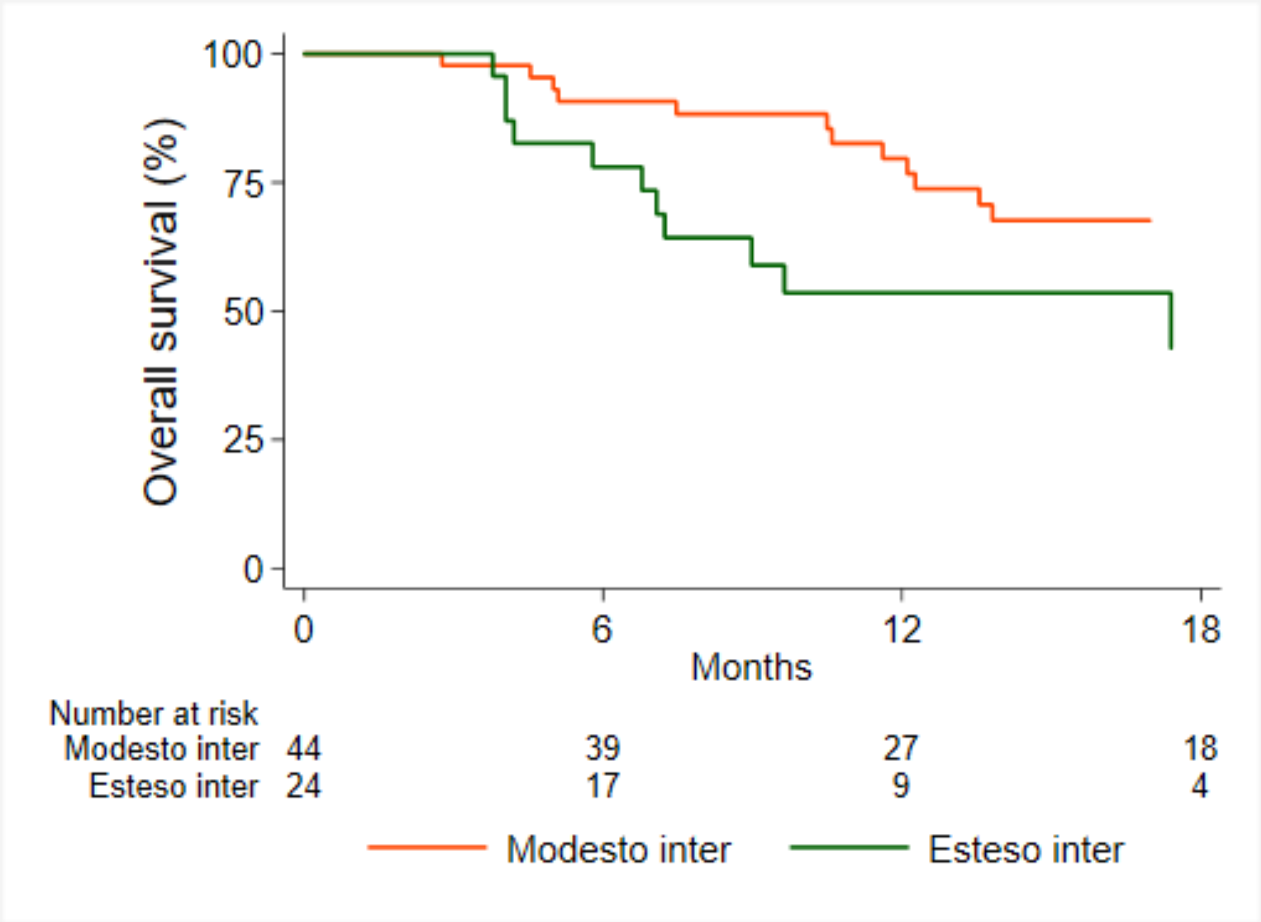


N=73 evaluable cases for progression-free survival

	Osso + G1 linfonodale	Osso + G2/3 linfonodi e parenchimi
N* of patients	48	25
N° of progressions	37	22
Median PFS (95%CI)	7.8 (6.4-10.4)	5.6 (3.9-7.0)
6 months PFS (95%CI)	66.4 (51.1-77.9)	40.7 (21.1-59.5)
12 months PFS (95%CI)	27.5 (15.2-41.3)	18.1 (5.7-36.0)

P-value (log-rank test): 0.029

Median Overall Survival



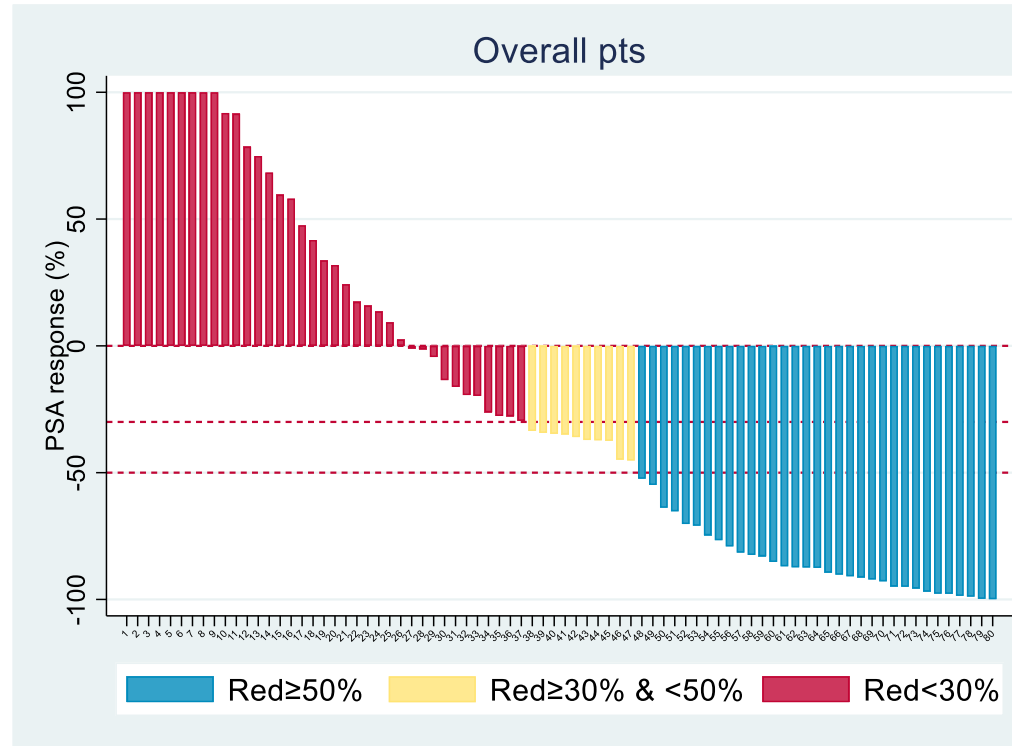
N=68 evaluable cases for overall survival

	Osso + G1 linfonodale	Osso + G2/3 linfonodi e parenchimi
N* of patients	44	24
N° of deaths	18	13
Median OS (95%CI)	27.3 (13.8-NE)	17.4 (7.1-19.2)
6 months OS (95%CI)	90.8 (77.2-96.4)	78.0 (54.9-90.2)
12 months OS (95%CI)	79.6 (63.2-89.3)	53.5 (30.6-72.0)

Median follow-up of overall case series: 20.6 months (range:2.7-35.2). **P-value (log-rank test): 0.005**
NE→ not estimable from statistical software

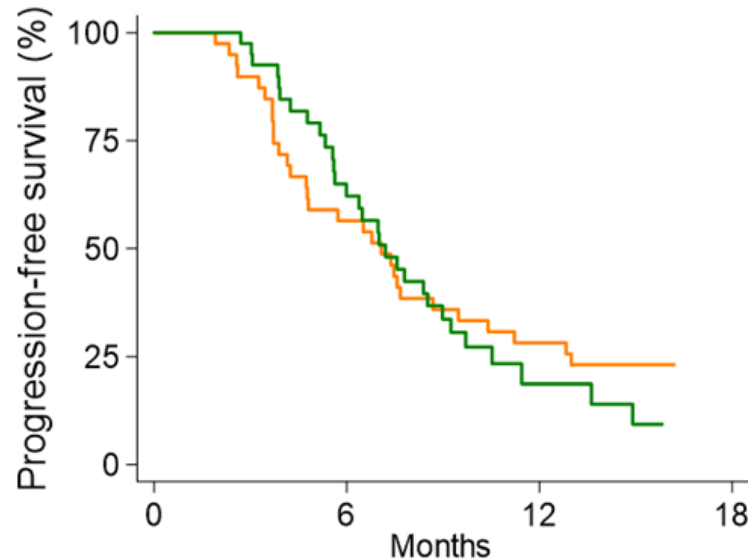


PSA biochemical response in 80 treated mCRPCs with ^{177}Lu –PSMA 3.7-5.5 GBq



- In 43 patients (53.7%) PSA reduction $\geq 30\%$
- Of these, 33 patients (41.3%) had PSA level above 50% after the 2nd cycle

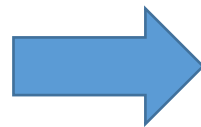
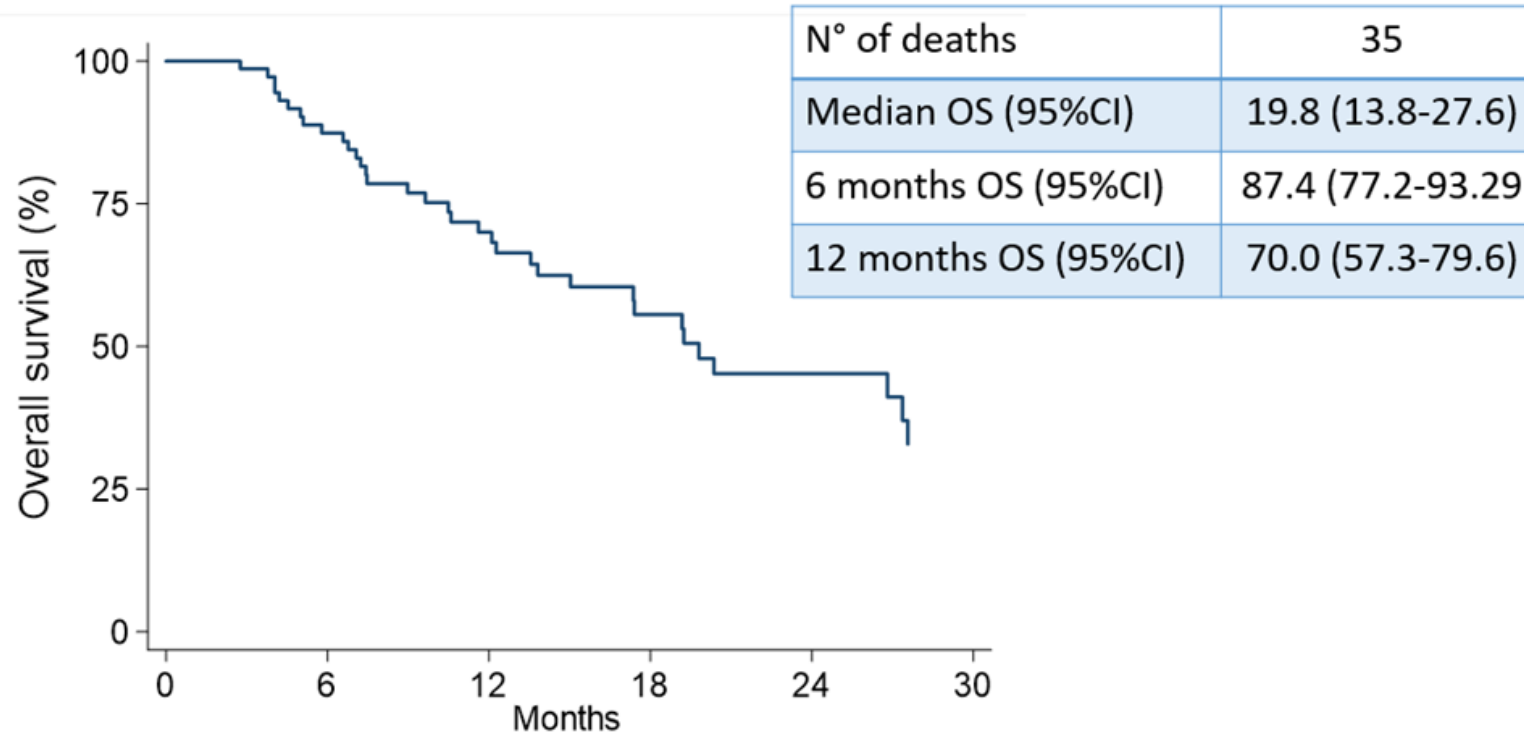
Progression-Free Survival



	3.7-4.4 GBq	5.5 GBq
N° of progressions	34	30
Median PFS (95%CI)	7.0 (4.2-9.5)	7.2 (5.6-8.9)
6 months PFS (95%CI)	56.4 (39.6-70.2)	62.1 (44.5-75.6)
12 months PFS (95%CI)	28.2 (15.2-42.7)	18.7 (7.1-34.5)

- Mean PFS is 7.0 months for the low dose group and 7.2 months for the higher dose group
- All together, 25% of patients had no disease progression at 12 months

Overall Survival



Considering the entire population, mOS is 19.8 months (13.8-27.6)



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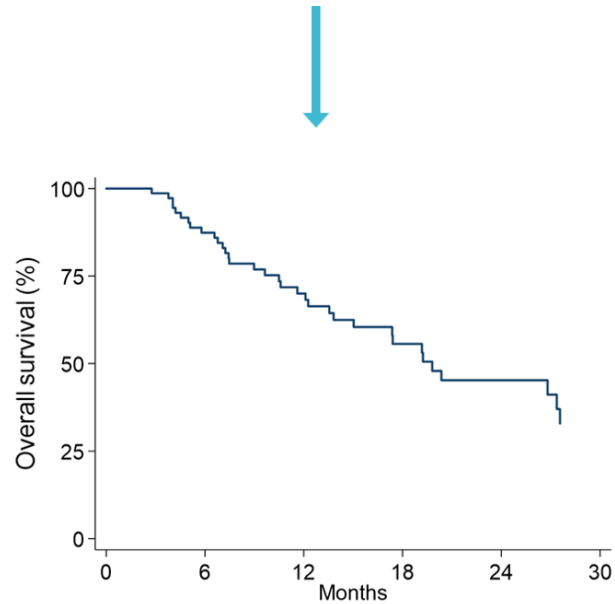
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Toxicity in 80 advanced mCRPC patients

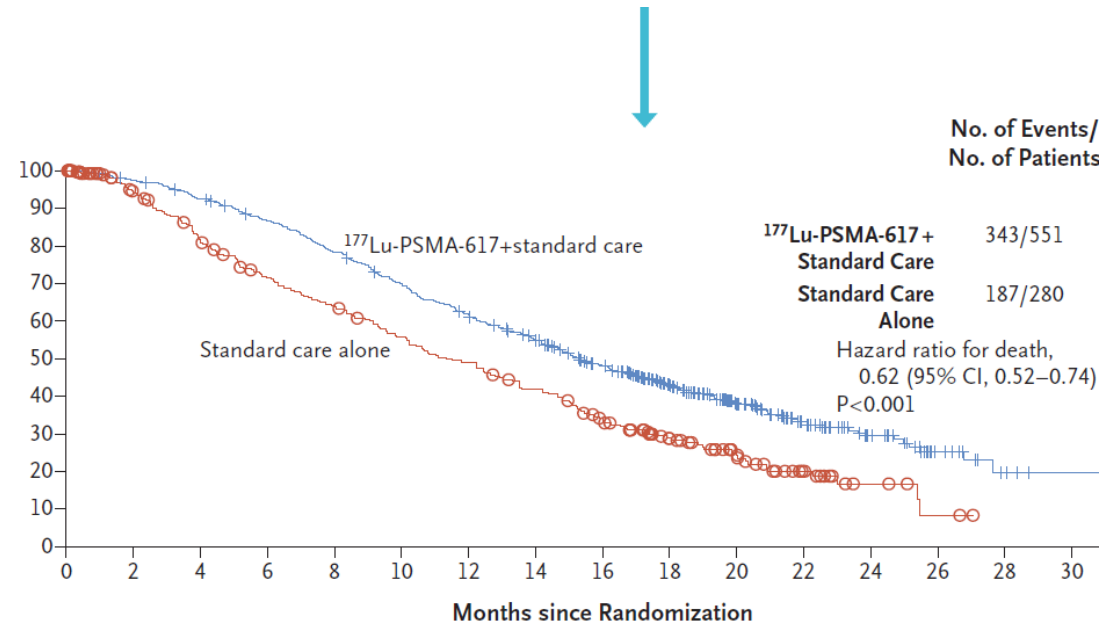
Event	Any toxicity No. Pts (%)	G1-G2 No. Pts (%)	G3 No. Pts (%)	G4 No. Pts (%)
Anemia	48 (60.0)	47 (58.7)	1 (1.3)	0 (0.0)
Thrombocytopenia	6 (7.5)	6 (7.5)	0 (0.0)	0 (0.0)
Neutropenia	8 (10.0)	7 (8.7)	1 (1.3)	0 (0.0)
Renal toxicity	18 (22.5)	16 (20.0)	2 (2.5)	0 (0.0)
Parotid gland toxicity	3 (3.8)	3 (3.8)	0 (0.0)	0 (0.0)



IRST



VISION



	IRST	VISION
Activity/Cycle (GBq)	3.7 – 5.5	7.4
G _{≥3} toxicity (%)	5	52.7
OS (months)	19.8	15.3



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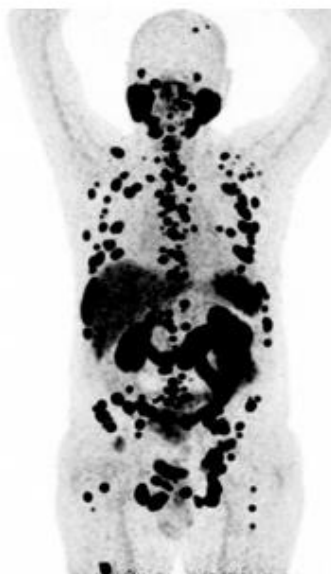


Pt n.H0624518, 67y, Adk prostate GS 7(3+4), 3 previous therapy lines,
baseline creatinine 4,3 **june 2019 creatinine 4.52**

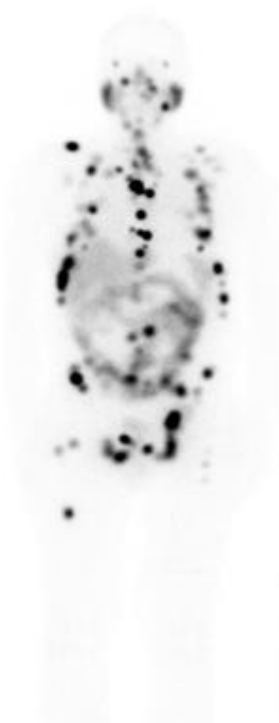
Sindrome di Berger (rene)

A double-blind
III, multicenter
treatment of
refractory pro

Sc
Pe

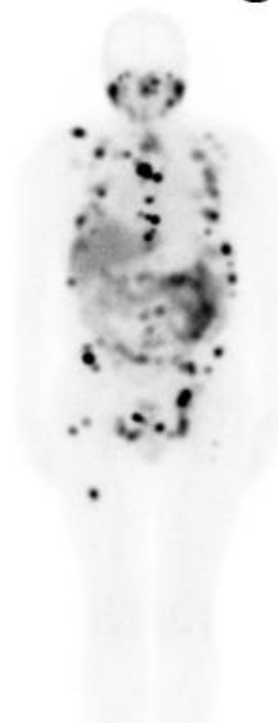


PET PSMA NOV 20



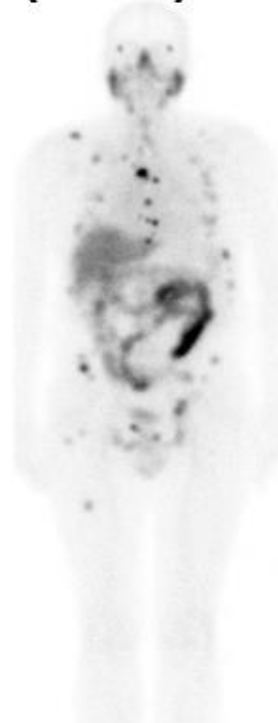
WBS DIC 2017

PSA 11.83



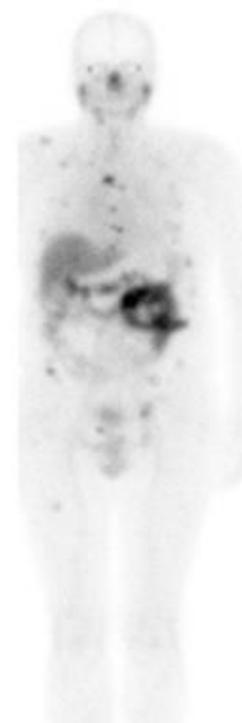
WBS FEB 2018

PSA 4.51



WBS APR 2018

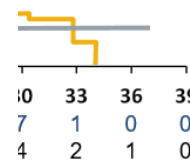
PSA 2.28



WBS GIU 2018

PSA 0.72

	Radium 223 + BSoC	Placebo + BSoC
OS	14.9	11.3
	0.70	
	0.58-0.83	
	<0.001	



ysis 30% reduction in
compared with placebo.

mCRPC patient selection for Lu-PSMA

High 68Ga PSMA uptake

FDG PET mismatch

Renal and medullary toxicity risk factors

Number of previous treatments

Load of skeletal / parenchymal disease

Plasma androgen receptors expression

Early biohumoral response

Early clinical response



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Team Work!!



stefano.severi@irst.emr.it



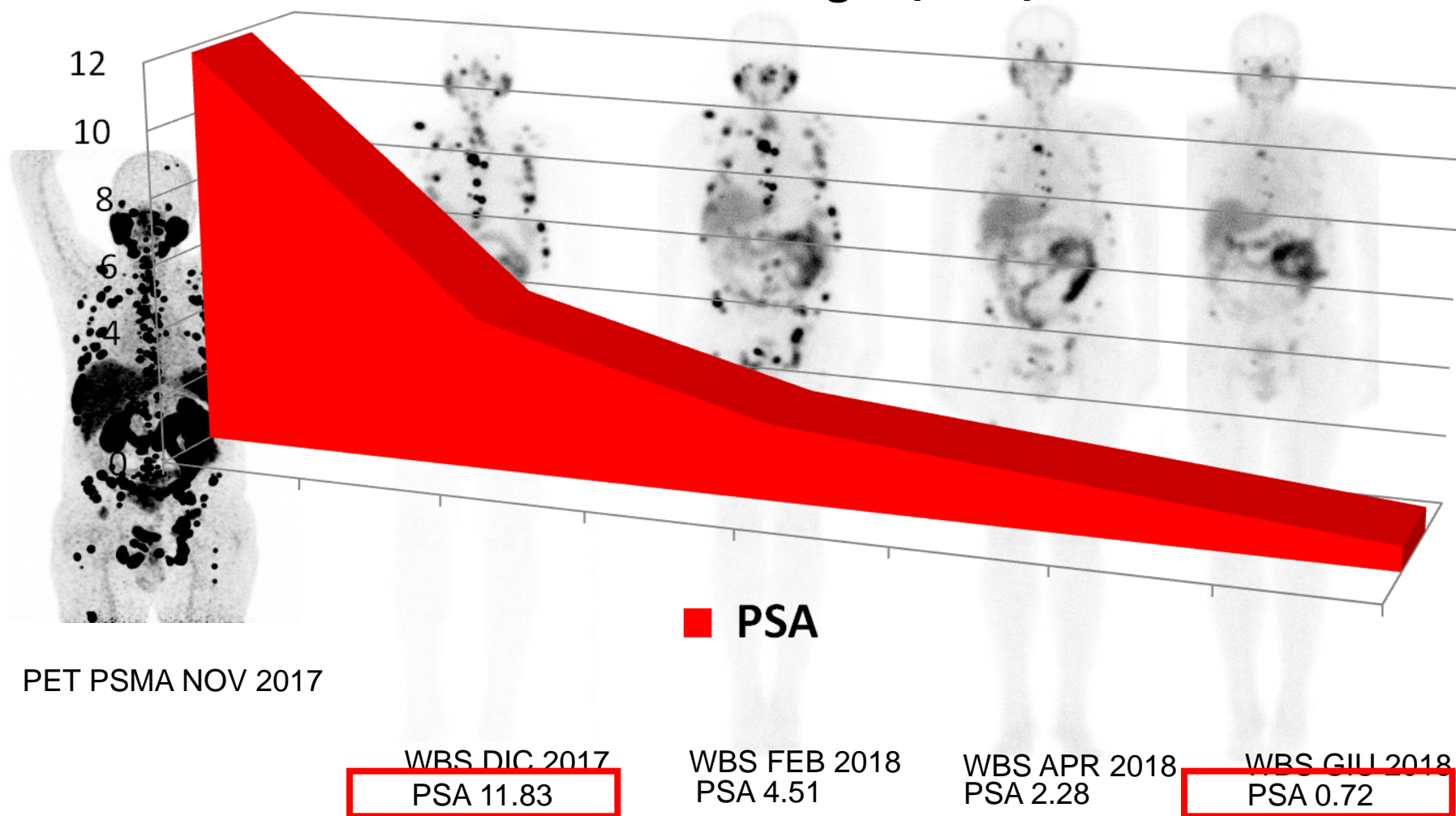
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Pt n.H0624518, 67y, Adk prostate GS 7(3+4), 3 previous therapy lines,
baseline creatinine 4,3 **june 2019 creatinine 4.52**

Sindrome di Berger (rene)



**4 cycle RLT 3,7GBq 177Lu-Dotatate, 6 cycles
223Ra Therapy and 2 cycles 225Ac PSMA therapy**

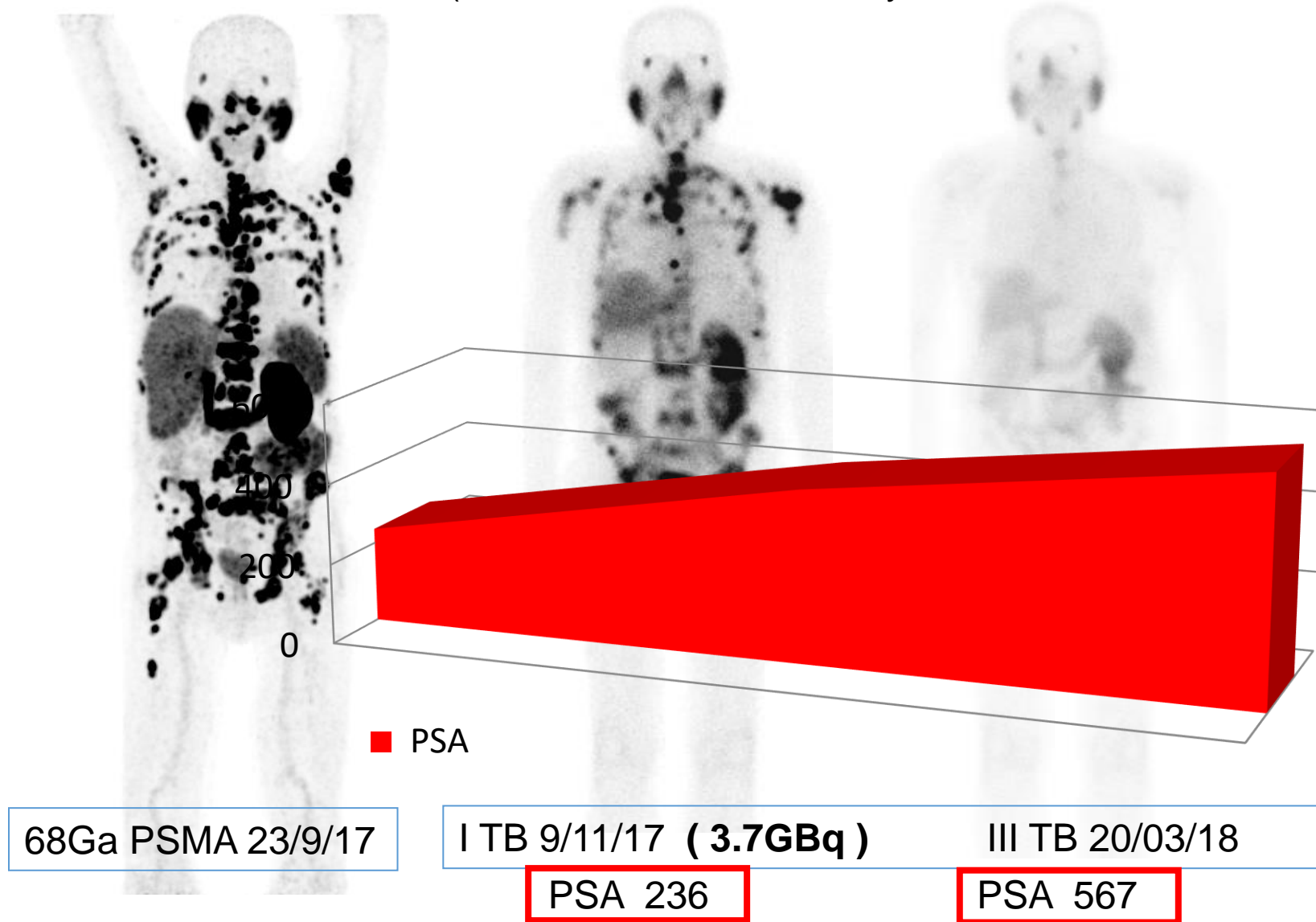


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2/5/34, Prostate cancer GS 8 (4+4), (pT4N0M0). Solitary Kidney, diabetic



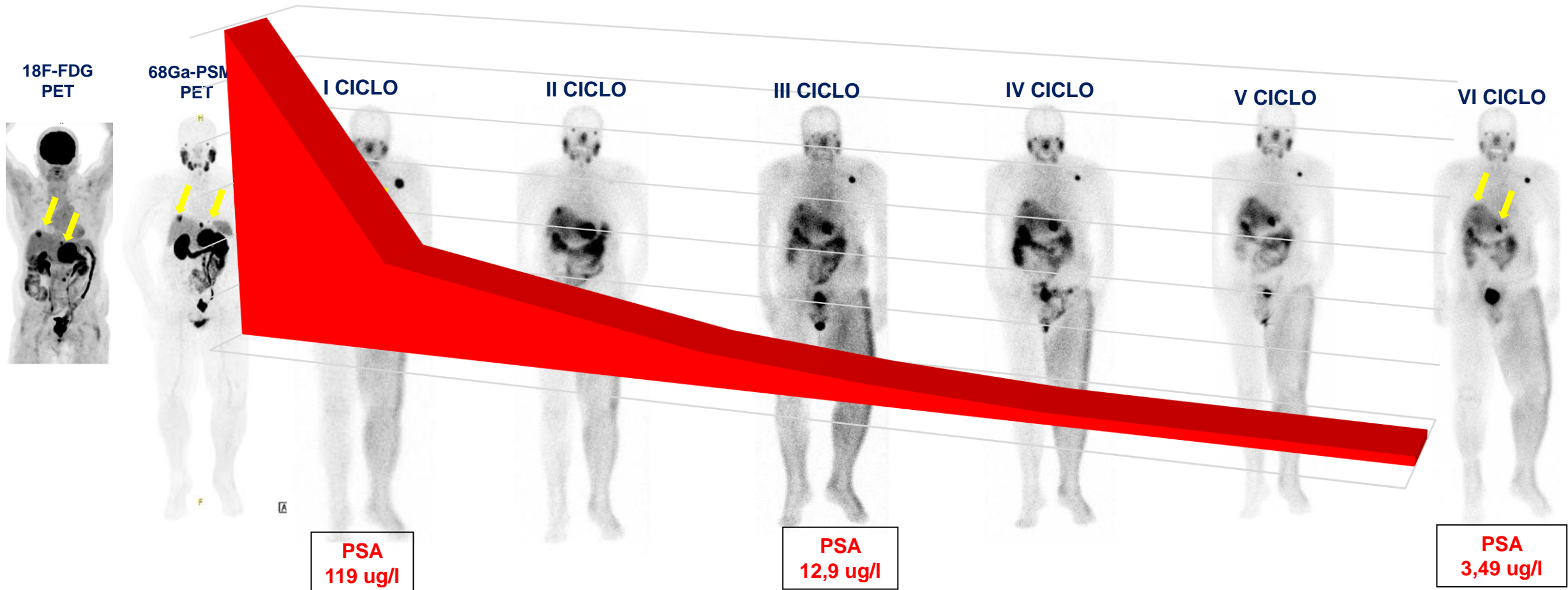
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Pt. 75 y – ECOG 0 – PROSTATE CANCER GS 8 (4+4) + METS LIVER and BONE
 several lines therapy, progressive disease

PSMA-PET + FDG-PET +



NON TOSSICITÀ EMATOLOGICA
 ToE RENALE >G1



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Organ at risk preservation

ACTIONS

Kidneys

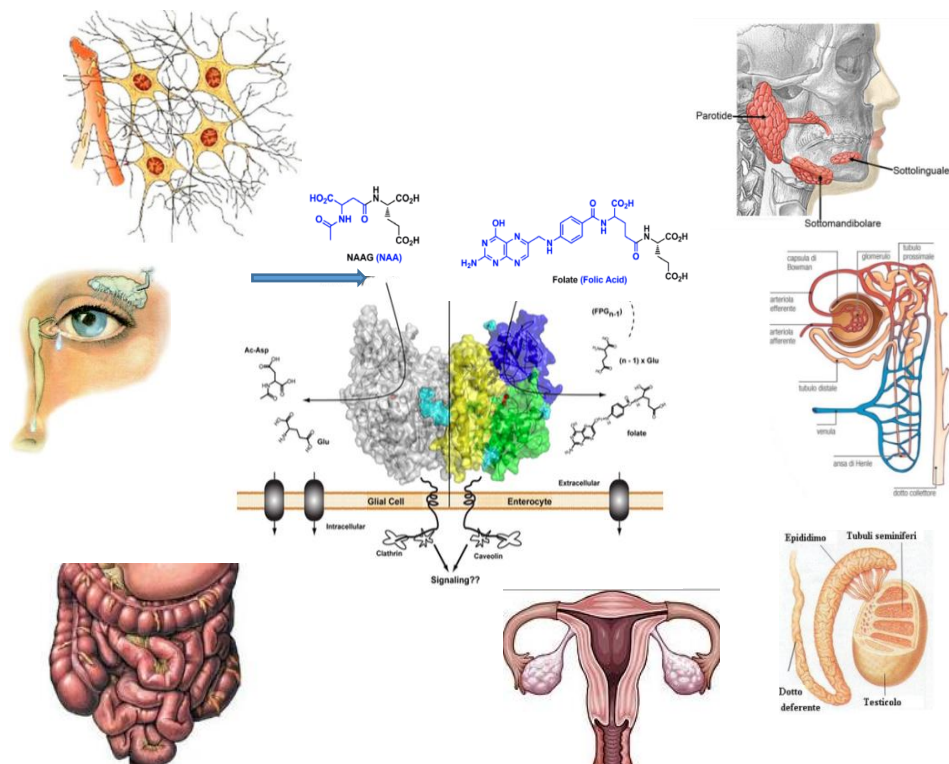
- ✓ 10% solution of mannitol*
Intravenously infused
- 250 ml @ 30 m before RLT
- 250 ml @ 60 m after RL

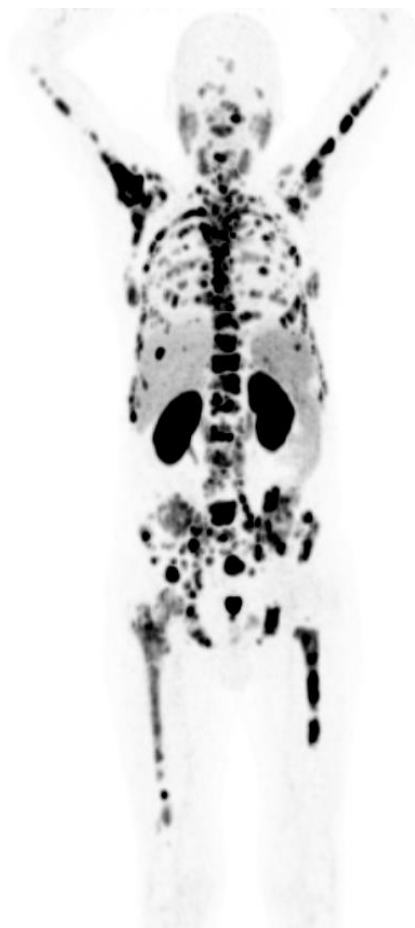
Salivary glands

- ✓ 2 folic polyglutamate candies before and during RLT
- ✓ Ice pack on the glands

Intestine

- ✓ Laxative solution
6h after RLT

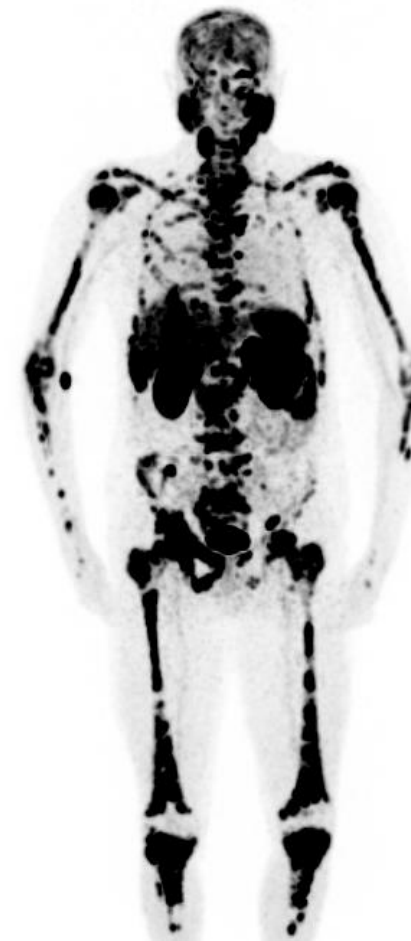




F. L. 24/7/1950.



S.B. 18/9/1953



P. I. 30/8/49



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Multidisciplinary team of Uroncology

Pathologist

Oncologist

Nurse

Radioterapist

Surgeon

Physicist



Biologist

Nuclear

Data Manager

Radiologist

Palliatologist

Radiology interventionist

Psychologist



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OPEN PSMA expression: a potential ally for the pathologist in prostate cancer diagnosis

Received: 27 October 2017

Accepted: 22 February 2018

Published online: 09 March 2018

Sara Bravaccini¹, Maurizio Puccetti², Martine Bocchini¹, Sara Ravaioli¹, Monica Celli³, Emanuela Scarpi⁴, Ugo De Giorgi⁵, Maria Maddalena Tumedei¹, Giandomenico Rauli², Loredana Cardinale² & Giovanni Paganelli³

Prostate cancer (PCa) patients are risk-stratified on the basis of clinical stage and PSA level at diagnosis and the Gleason Score (GS) in prostate biopsy. However, these parameters are not completely accurate in discriminating between high- and low-risk disease, creating a need for a reliable marker to determine aggressiveness. Prostate-specific membrane antigen (PSMA) appears to fulfill this need. We analyzed 79 prostate biopsies and 28 prostatectomies to assess whether PSMA expression detected by immunohistochemistry is related to GS. PSMA expression was correlated with GS in both sample types (biopsies, $P < 0.0001$ and prostatectomy samples, $P = 0.007$). We observed lower PSMA expression in Gleason pattern 3 than Gleason pattern 4, suggesting that this biomarker could be useful to distinguish between these entities ($p < 0.0001$). The best cut-off value of 45% immunopositivity was determined by receiver operating characteristic (ROC) curve analysis. In Gleason pattern 3 vs. Gleason pattern 4 and 5, PSMA sensitivity was 84.1% (95% CI 76.5%-91.7%) and specificity was 95.2% (95% CI 90.6%-99.8%), with an area under the curve of 93.1 (95% CI 88.8–97.4). Our results suggest that PSMA represents a potential ally for the pathologist in the diagnostic work-up of PCa to overcome long-standing morphological classification limits.



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