Forum Risk Management
obiettivo sanità salute
26-29 NOVEMBRE 2024
AREZZO FIERE E CONGRESSI
19

Evoluzione della medicina nucleare a livello di Area Vasta per la definizione di nuovi radiofarmaci per la diagnosi e cura. Gestire il problema della malattia oncologica dalla radioterapia tradizionale alla medicina personalizzata

Prof. Isacco Desideri

Università di Firenze

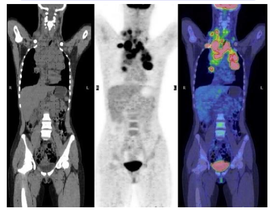
SODc Radioterapia AOU Careggi

#ForumRisk19
www.forumriskmanagement.it

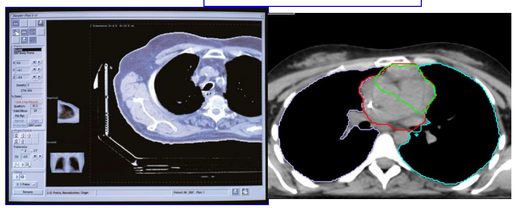
Targeted Radionuclide Therapy

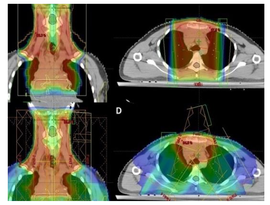
- ✓Is tumor specific, with sparing of healthy tissue (low toxicity)
- ✓No limit to the absorbed dose
- ✓Radiation can be delivered to any numer of sites of disease
- ✓Radiation can be delivered to subclinical tumors and metastases that are too small to be imaged
- ✓Radiation can be delivered to cells in the circulating blood including hematologic malignancy

Imaging di stadiazione

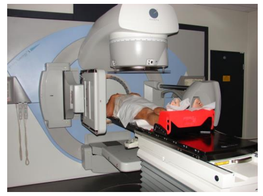


Contornazione CTV/PTV/OAR

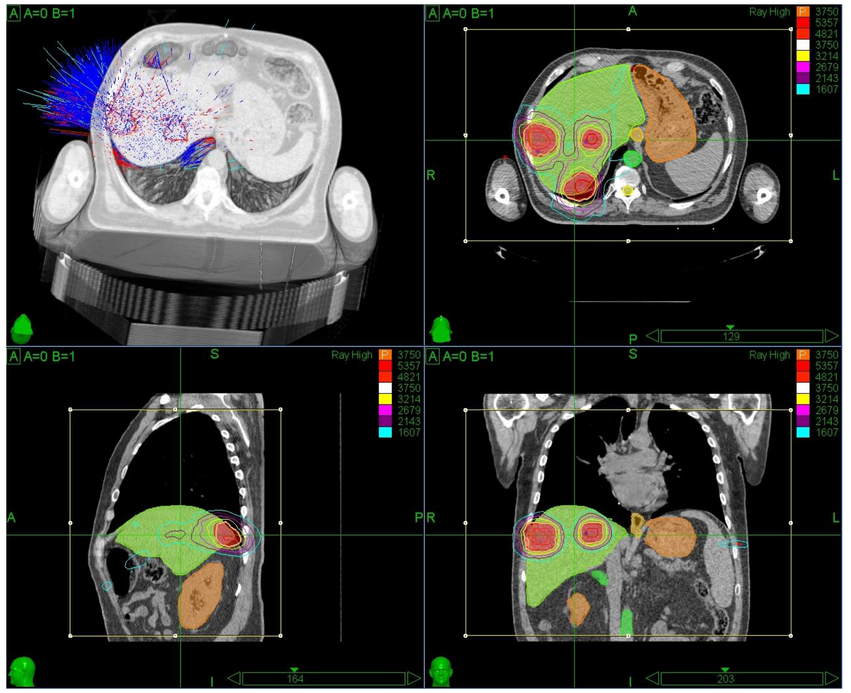


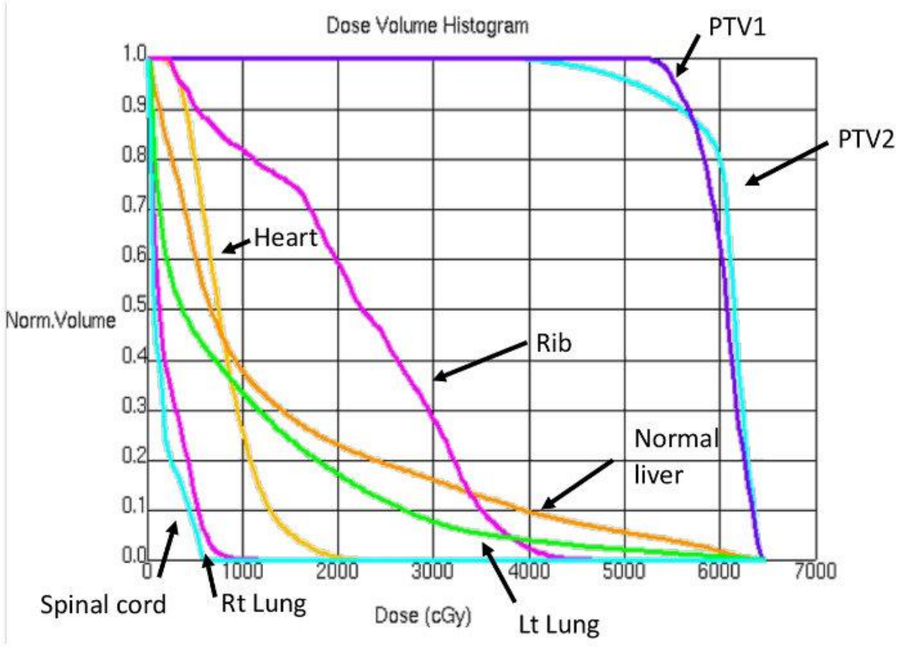


Realizzazione del piano e decisione della tecnica di trattamento



Trattamento


A A=0 B=1
A A=0 B=1
A
Ray High
3750
5357
4821
3750
3214
2679
2143
1607
R
L
P
129
A A=0 B=1
S
Ray High
A
P R
164
A A=0 B=1
S
Ray High
P R
L
203


Dose Volume Histogram
PTV1
PTV2
Heart
Rib
Normal liver
Norm.Volume
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1000
2000
3000
4000
5000
6000
7000
Spinal cord
Rt Lung
Dose (cGy)
Lt Lung

SBRT: prospective studies

STUDY	PATIENTS	LESIONS	RT DOSE	OUTCOME
Herfarth et al, 2004 *Phase I/II*	35	51	14/26 Gy in 1 fr	**18 months:** **67%**
Mendez et al, 2006 *Phase I/II*	17	34	30/37.5 Gy in 3 fr	**2-year: 86%**
Hoyer et al, 2006 *Phase II*	44 (only CRC)	NA	45 Gy in 3 fr	**2-year: 79%**
Lee et al, 2009 *Phase I/II*	68	140	28/60 Gy in 6 fr	**1-year: 71%**
Rusthoven et al, 2009 *Phase I/II*	47	63	36/60 Gy In 3 fr	**2-year: 92%**
Goodman et al, 2010 *Phase I*	19	33	18/30 Gy in 1 fr	**1-year: 77%**
Rule et al, 2011 *Phase I*	26	35	30 Gy in 3fx 50 Gy in 5fx 60 Gy in 3fx	**2-year: 56%** **2-year: 89%** **2-year: 100%**

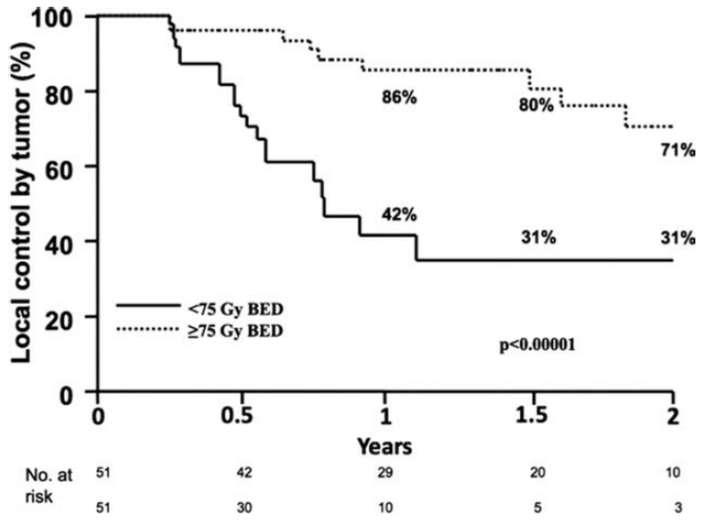


Figure 2. Actuarial local control by lesion stratified by biologically effective dose (BED) delivered is shown.

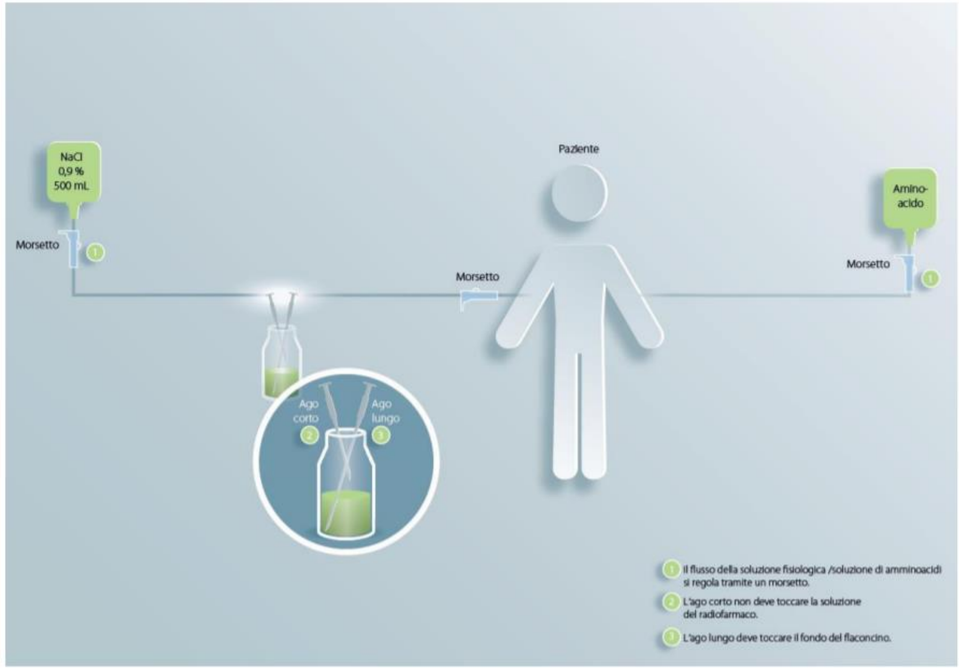
Chang, Cancer 2011

LIVER SBRT – Dose constraints

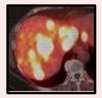
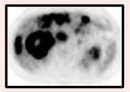
Organ at risk	Wulf *et al.* (36)	Rusthoven *et al.* (37)	Hoyer RAS–Trial (www.cirro.dk)	RTOG 0236 SBRT lung (www.rtog.org)	QUANTEC (48)
Liver (CTV excluded)	30% <21 Gy* 50% <15 Gy*	700 mL < 15 Gy	700 mL < 15 Gy	NA	700 mL ≤15 Gy D_{mean} < 15 Gy
Stomach	$D_{5\ mL}$ <21 Gy	D_{max} ≤30 Gy	$D_{1\ mL}$ <21 Gy	NA	D_{max} <30 Gy ($D_{5\ mL}$ <22.5 Gy)
Bowel	$D_{5\ mL}$ <21 Gy	D_{max} ≤30 Gy	$D_{1\ mL}$ <21 Gy	NA	D_{max} <30 Gy
Esophagus	$D_{5\ mL}$ <21 Gy	NA	$D_{1\ mL}$ <21 Gy	D_{max} ≤27 Gy	NA
Kidney	NA	Total kidney $D_{35\%}$ <15 Gy	Total kidney $D_{35\%}$ <15 Gy	NA	NA
Spinal cord	NA	D_{max} ≤18 Gy	D_{max} <18 Gy	D_{max} ≤18 Gy	D_{max} ≤20 Gy
Heart	$D_{5\ mL}$ <21 Gy	NA	$D_{1\ mL}$ <30 Gy	D_{max} ≤30 Gy	NA

Abbreviations: SBRT = stereotactic body radiotherapy; RTOG = Radiation Therapy Oncology Group; CTV = clinical target volume; NA = not available; Dx % = dose to x%; Dx mL = dose to x mL; D_{max} = maximum dose.
* Liver including clinical target volume.

Hoyer M et al, IJROBP, 2012


NaCl
0,9 %
500 mL
Morsetto
1
Paziente
Morsetto
Amino-
acido
Morsetto
1
Ago
corto
2
Ago
lungo
3
1 Il flusso della soluzione fisiologica /soluzione di amminoacidi si regola tramite un morsetto.
2 L'ago corto non deve toccare la soluzione del radiofarmaco.
3 L'ago lungo deve toccare il fondo del flaconcino.

Diagnostic Imaging for TherapeuticDecision-Making

Tumor Grade	Differentiation	SSTR-2 Expression	Imaging Modality
Grade 1, Low	Well-Differentiated	High 	^{68}Ga-Dotatate 
Grade 2, Intermediate	Well-Differentiated	Mixed 	^{68}Ga-Dotatate and ^{18}F-FDG  
Grade 3, High (Neuroendocrine Carcinoma)	Poorly Differentiated	Low/ Zero 	^{18}F-FDG 

Dual Imaging of PET Radiotracers
(Chan, et al *Theranostics 2017*)

- Allows for ***whole-body tumor grading*** and assessment of ***tumor heterogeneity***
- ***Non-invasive tumor characterization*** can help clinicians determine the next appropriate treatment option

Adapted from and slide courtesy of Amanda Abbott, MS, CNMT, RT(N)(CT), PET and Lauren Gilbert, CNMT, RT(N)(CT)
Grading and Prognostication of Neuroendocrine Tumors of the Pancreas: A Comparison Study of Ki67 and PHH3

BED: Biologically Effective Dose

$$BED = nd\left(1 + \frac{d}{[\alpha/\beta]} - \log_e 2\frac{(T-Tk)}{\alpha Tp}\right)$$

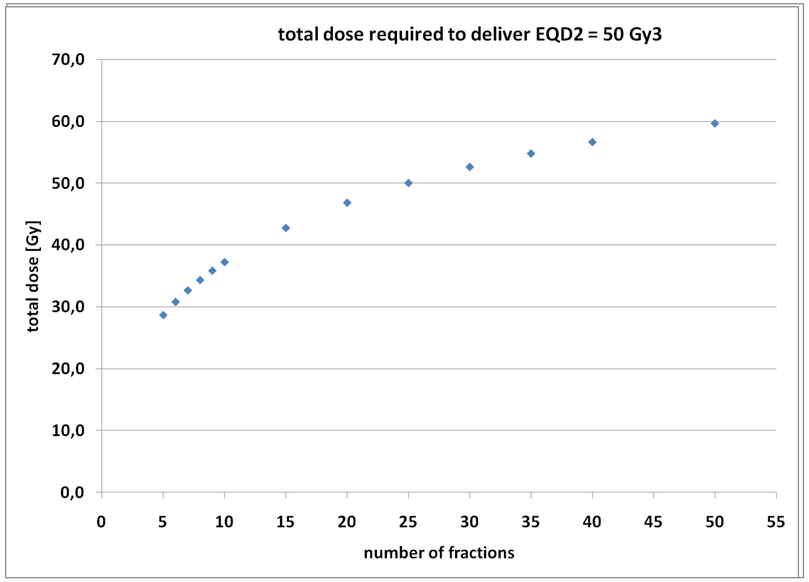
nd=total dose

T=overall time

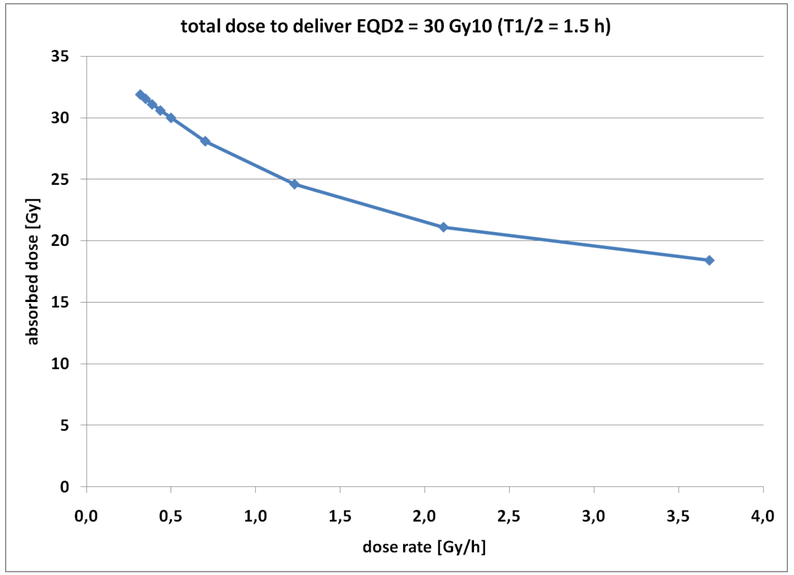
Tumour repopulation
Tk:kick off time
Tp:cell doubling time

- it indicates quantitatively the biological effect of any radiotherapy treatment, taking account of changes in dose-per-fraction or dose rate, total dose and overall time.

The linear-quadratic model:
Fractionation sensitivity

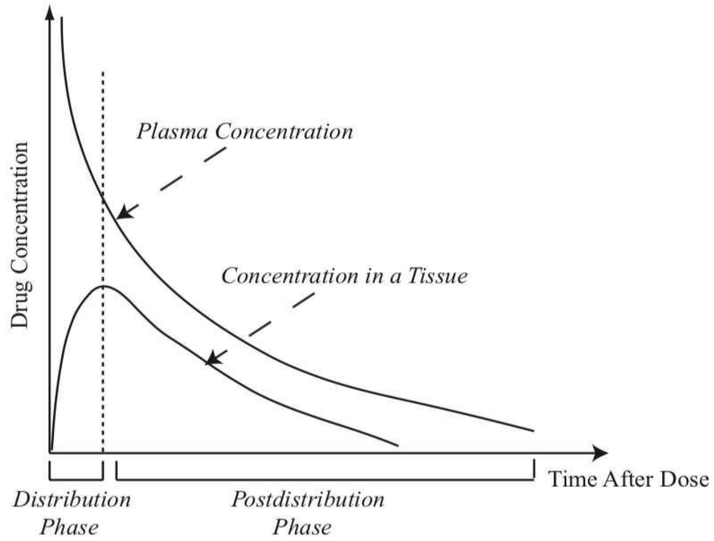


The linear-quadratic model:
Dose rate effect



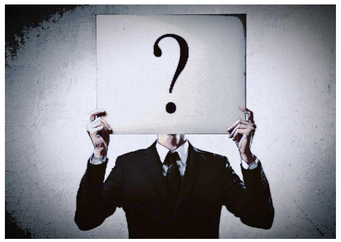
Pharmacokinetics

- Interactions of drug and body in terms of
  - Absorption (if oral)
  - Distribution
  - Metabolism
  - Excretion



Tumor Response to Radiopharmaceutical Therapies: The Knowns and the Unknowns

George Sgouros[1], Yuni K. Dewaraja[2], Freddy Escorcia[3], Stephen A. Graves[4], Thomas A. Hope[5], Amir Iravani[6], Neeta Pandit-Taskar[7], Babak Saboury[8], Sara St. James[5], and Pat B. Zanzonico[9]



J Nuc Med, 2021

TABLE 3
Studies Reporting Tumor Dose–Response Relationship in Other RPTs

Study	Disease	Therapy	*n*	Lesion size	Dosimetry method	Endpoint	Threshold
Maxon (*139*)	Thyroid cancer metastases	^{131}I radioiodine	76		Planar conjugate views	Response on ^{131}I planar scans	80 Gy for metastases; 300 Gy for remnants
Wierts (*140*)	Thyroid cancer remnants and metastases	^{131}I radioiodine	47	>0.15 cm^3	^{124}I PET + OLINDA sphere model	CR on ^{131}I SPECT or ^{124}I PET	40 Gy for metastases; 90 Gy for remnants
Pauwels (*102*)	NET	^{90}Y-DOTATOC PRRT	13	NA	^{86}Y-DOTATOC PET + MIRDOSE sphere model	Volume shrinkage > 30% on CT	~150 Gy for >30% shrinkage
Ilan (*103*)	NET	^{177}Lu-DOTATATE PRRT	24 (24 tumors)	>2.2 cm	SPECT/CT + OLINDA sphere model	RECIST best response > 30%	~150 Gy
Matthay (*141*)	Neuroblastoma	^{131}I-metaiodobenzylguanidine	27		Planar conjugate view + MIRDOSE	Volume shrinkage > 50% on CT	70 Gy
Dewaraja (*16*)	Non-Hodgkin lymphoma	^{131}I-radioimmunotherapy	39 (130 tumors)	Median, 20 cm^3	Multi-SPECT/CT + Monte Carlo	Progression-free survival	200 cGy

Dose Response of Pancreatic Neuroendocrine Tumors Treated with Peptide Receptor Radionuclide Therapy Using ^{177}Lu-DOTATATE

Ezgi Ilan[1,2], Mattias Sandström[1,2], Cecilia Wassberg[1,3], Anders Sundin[1,3], Ulrike Garske–Román[1,3], Barbro Eriksson[4], Dan Granberg[4], and Mark Lubberink[1,2]

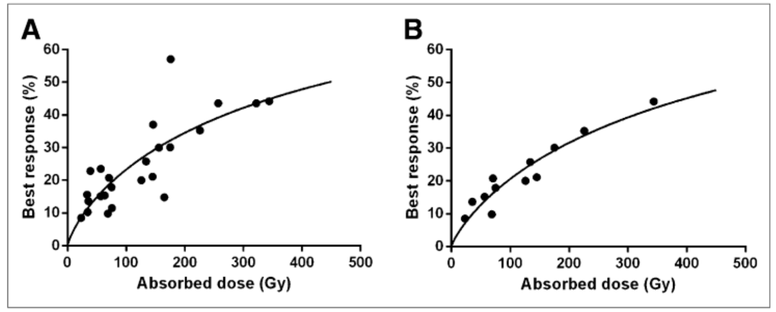


FIGURE 5. Tumor dose–response relationship for patients with PNETs treated with PRRT using ^{177}Lu-DOTATATE, including tumors larger than 2.2 cm (A) and only tumors larger than 4 cm (B). Solid lines represent 2-parameter sigmoid fits ($y = 100/(1+ (\alpha/x)^{\beta})$), where α and β are fitting parameters. Parameters α and β were 445 and 0.79, with SEs of 104 and 0.14, respectively, for tumors larger than 2.2 cm and 504 and 0.84, with SEs of 83 and 0.1, respectively, for tumors larger than 4 cm. Pearson correlation coefficients (R^2) were 0.64 (A) and 0.91 (B).

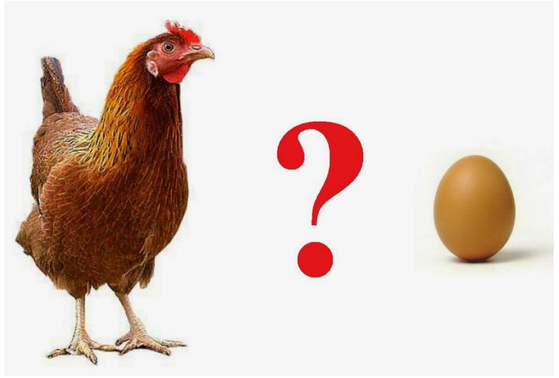
CONTINUING EDUCATION

Dosimetry in Radiopharmaceutical Therapy

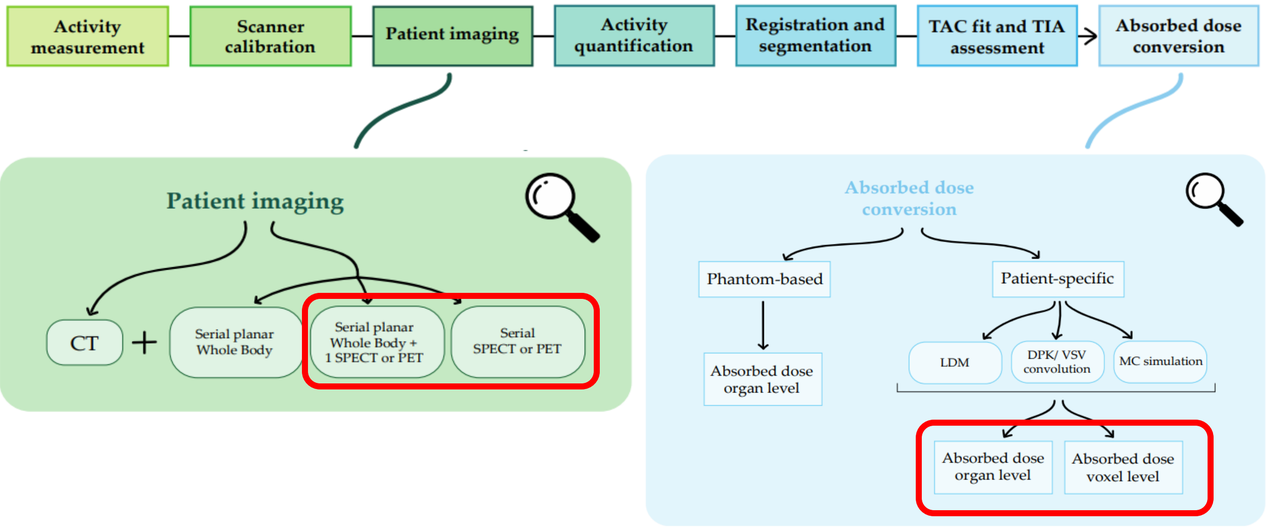
Joe O'Donoghue, Pat Zanzonico, John Humm, and Adam Kesner

Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, New York

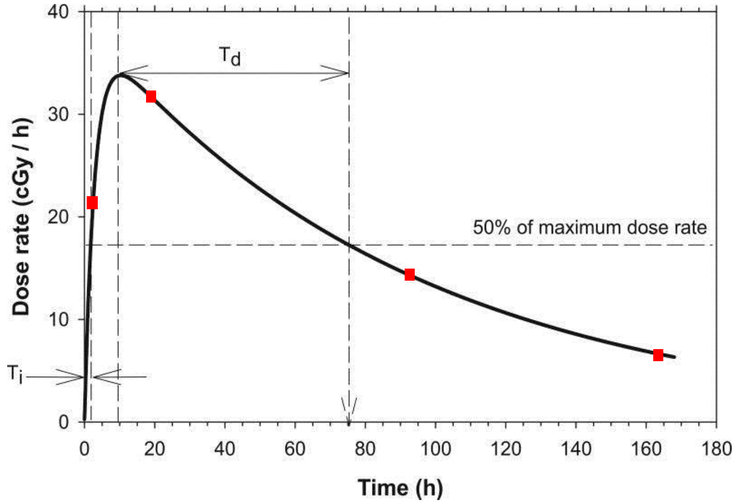
"...there is a chicken-and-egg element to this: dosimetry is not performed because dose–response data are lacking, and dose–response data are lacking because dosimetry is not performed..."



DOSIMETRY WORKFLOW



Adapted from Danieli, J Pers Med 2022



Acquisition Number	Approximate Post-therapy Acquisition Time
1	4 hours
2	24 hours
3	96 hours
4	168 hours

Radiation Research 188: 221-234, 2017

Table 2
List of commercially available MRT dosimetry software and referring versions. *previously known as Hermes Internal Radiation Dosimetry / HIRD / Hybrid3Dose / HybridDose3D.

TPS	Manufacturer	Abbreviation	Dosimetry Type	CE/FDA approval
Organ Dosimetry with Olinda/EXM® v5.1 (Olinda v2.2)	Hermes Medical Solutions	HERMES Organ	Multi-purpose Organ Dosimetry	CE/FDA
Voxel Dosimetry* v1.0.1	Hermes Medical Solutions	HERMES Voxel	Multi-purpose voxel dosimetry	CE/FDA
Planet® Dose v3	DOSIsoft SA	PlanetDose	Multi-purpose voxel dosimetry	CE/FDA
QDOSE® v1.1	ABX-CRO advanced pharmaceutical Forschungsgesellschaft mbH	QDose	Multi-purpose voxel dosimetry	CE
SurePlan™ MRT v7.1	MIM Software Inc.	SurePlan-MRT	Multi-purpose voxel dosimetry	CE/FDA

Della Gala, Eur J Med Phys 2021

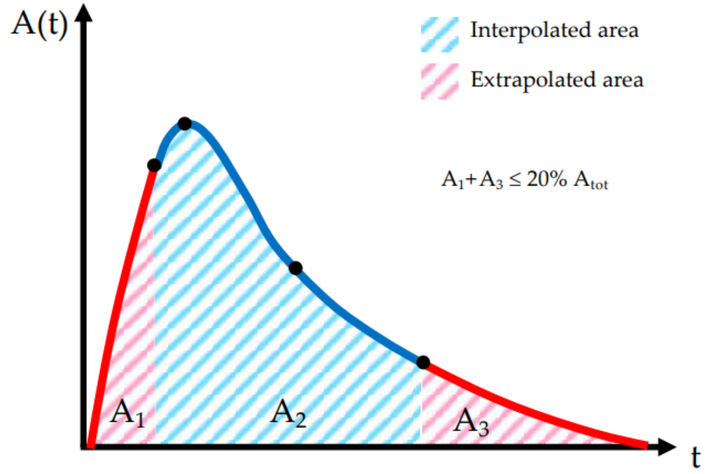
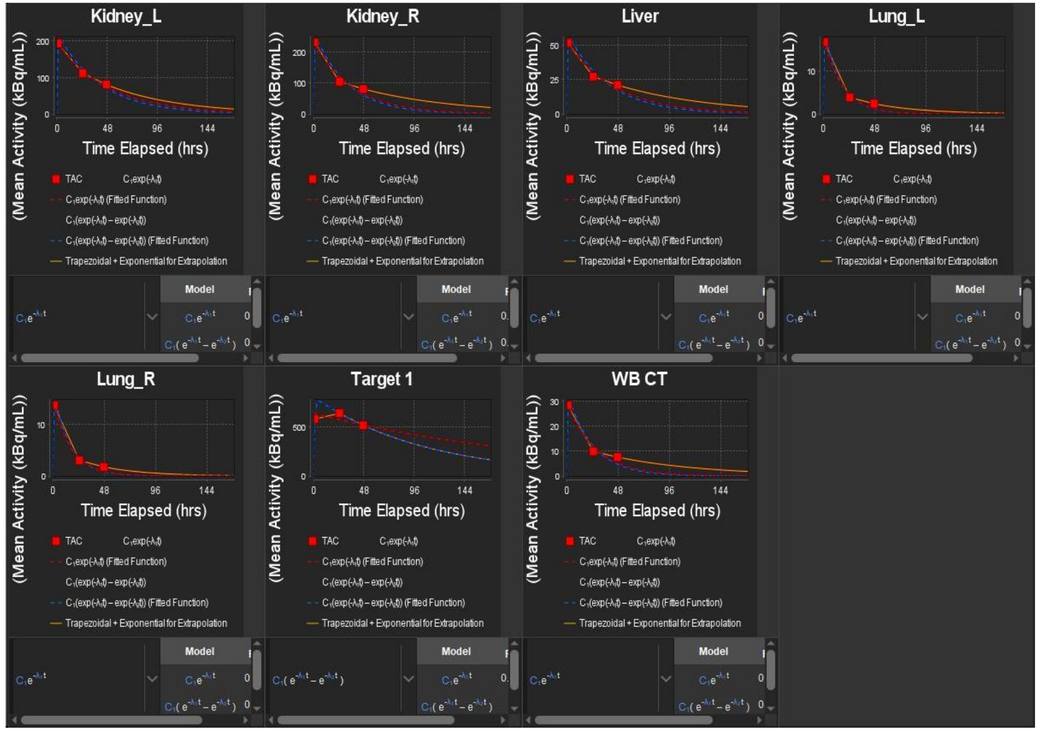
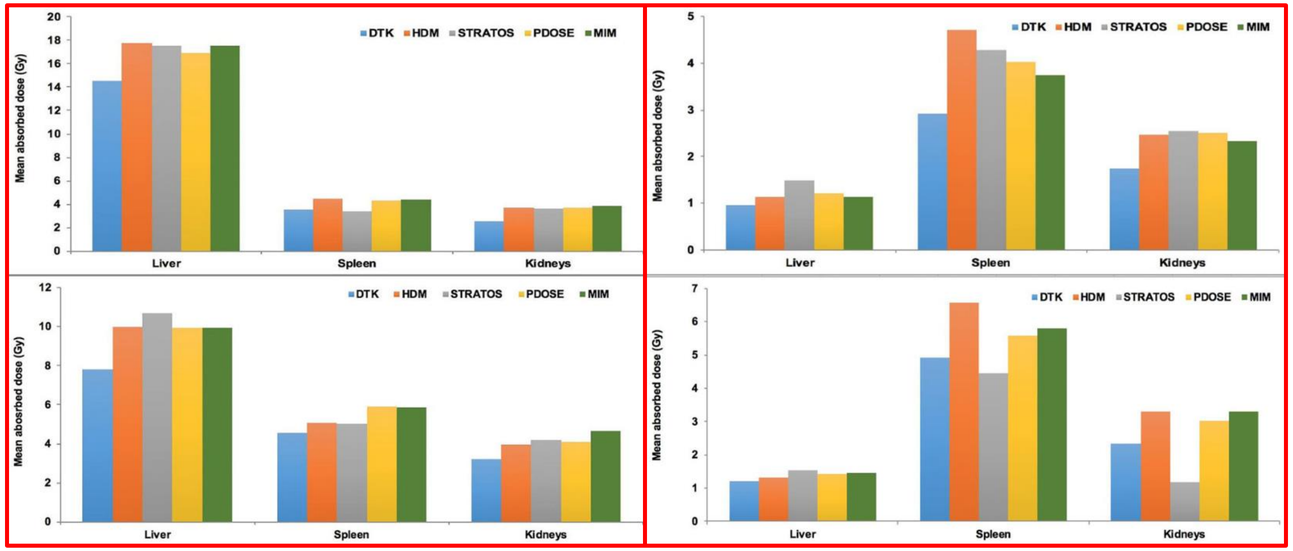


Figure 2. Time–activity curve (TAC) with interpolation and extrapolation areas.

Danieli, J Pers Med 2022


Contours
Select a Series to Contour
2018 07-11
Dose SPECT
FENET007
NOT FOR CLINICAL USE: AC Recon
Mode Tools
PET Edge
PET Edge+
Whole Body
Region Grow
Threshold
Pen
2D Brush
3D Brush
2D Fill
Move
Circular Contour
Copy Contour
Point Contour
Rectangular Contour
Atlas Segment
Kidney_L
Kidney_R
Kidneys
Liver
Lung_L
Lung_R
Lungs
Rest of Body
Target 1
WB
CT2a - PRI 1, 7
FENET007
Reference CT
AC AbdRoutine 5.0 B08s
ANON31409
2018-07-11 14:10:09
NM2c - SEC 7
Dose SPECT
CT/NM Fusion #1
Fusion 3


Kidney_L
Kidney_R
Liver
Lung_L
Lung_R
Target 1
WB CT
(Mean Activity (kBq/mL))
Time Elapsed (hrs)
TAC
Trapezoidal + Exponential for Extrapolation
Model



...relative standard deviations in mean absorbed doses, on average are<16%, with a maximum at 41%

MedPhys, 2020

European Journal of Nuclear Medicine and Molecular Imaging (2018) 45:2456–2474
https://doi.org/10.1007/s00259-018-4136-7

GUIDELINES

EANM practical guidance on uncertainty analysis for molecular radiotherapy absorbed dose calculations

Jonathan I. Gear[1] · Maurice G. Cox[2] · Johan Gustafsson[3] · Katarina Sjögreen Gleisner[3] · Iain Murray[1] · Gerhard Glatting[4] · Mark Konijnenberg[5] · Glenn D. Flux[1]

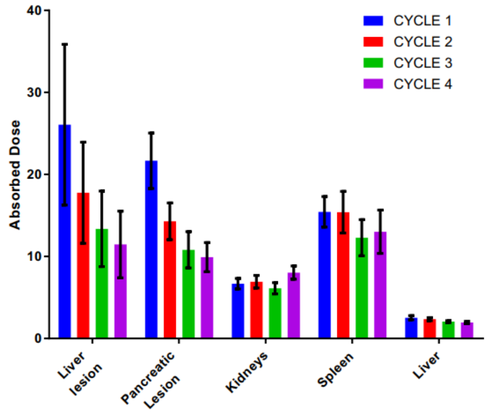


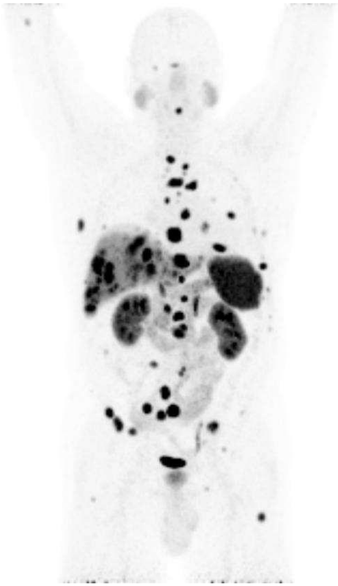
Fig. 12 Absorbed doses to lesions and normal organs over four treatment cycles. *Error bars* represent standard uncertainties in the dose values

- Posso predire l'efficacia della terapia già dall'imaging?
- Posso predire l'efficacia della terapia dalla dosimetria della prima somministrazione? E la tossicità?
- Stessa dose per tutti… Siamo sicuri di trattare adeguatamente i nostri pazienti?

Eligibility for therapy

- Uptake in lesions
  above the liver uptake

Score	Intensity
0	None (no uptake)
1	Very low
2	Less than or equal to that of liver
3	Greater than that of liver
4	Greater than that of spleen



Dosimetry of ^{177}Lu-P
Resistant Prostate Ca
Pretherapeutic Imagi
with Treatment Outc

John Violet[1], Price Jackson[1,2], Justin Ferd
Aravind Ravi Kumar[2], Sue Ping Thang[2],
Rodney J. Hicks[2,5], and Michael S. Hofm

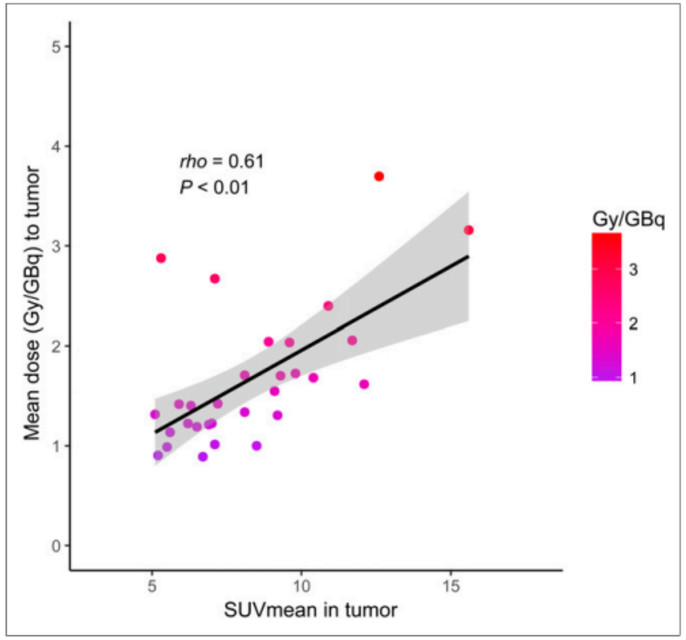
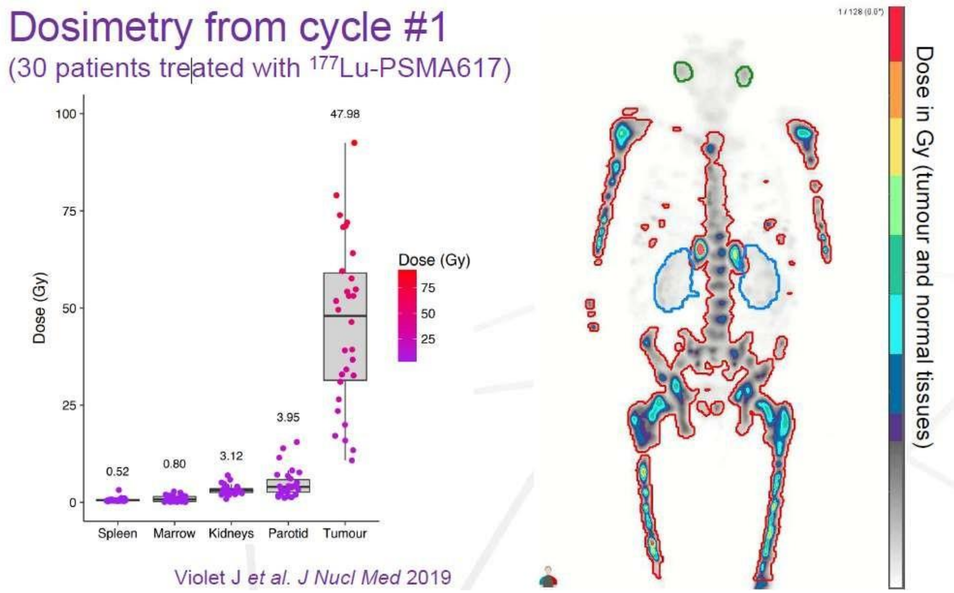
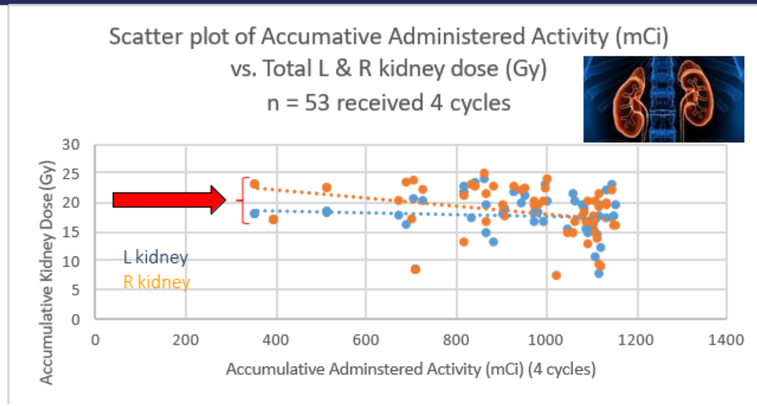


FIGURE 5. Correlation between SUV_{mean} on screening ^{68}Ga-PSMA PET and mean whole-body tumor dose calculated using 5-Gy dose cutoff.

Molecular and volumetric parameters using an automated voxel-based dosimetry tool



Dose delivered to normal structures – kidneys



- 68% of pts received an accumulative escalated dose (≥880mCi)
- Dose escalation achieved while maintaining renal tolerance
- Accumulated dose maintained below 23Gy in all pts except 1
- Median accumulated renal dose 18 (SD4) Gy

European Journal of Nuclear Medicine and Molecular Imaging (2022) 49:3830–3840
https://doi.org/10.1007/s00259-022-05786-w

ORIGINAL ARTICLE

Check for updates

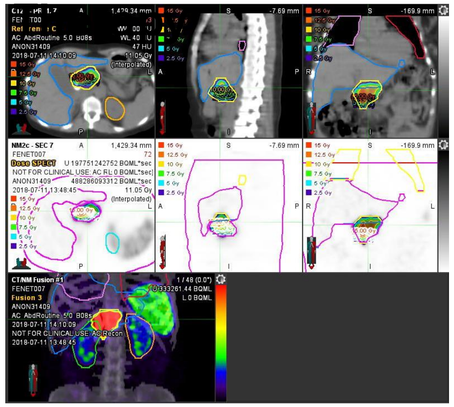
Phase II trial demonstrates the efficacy and safety of individualized, dosimetry-based ^{177}Lu-DOTATATE treatment of NET patients

Anna Sundlöv[1] · Katarina Sjögreen Gleisner[2] · Jan Tennvall[1] · Michael Ljungberg[2] · Carl Fredrik Warfvinge[1] · Kajsa Holgersson[3] · Andreas Hallqvist[3,4] · Peter Bernhardt[5,6] · Johanna Svensson[3,4]

- All patients were planned for treatment up to a cumulative renal BED of 27±2 Gy (step 1).

- Thereafter, patients complying with the inclusion and exclusion criteria for step 2 (GFR>50 ml/min with a maximum decrease of 40% from baseline, no grade 3–4 toxicity, and a maximum age of 70 years) were offered further treatment up to a renal BED of 40±2 Gy.

RadioLigand



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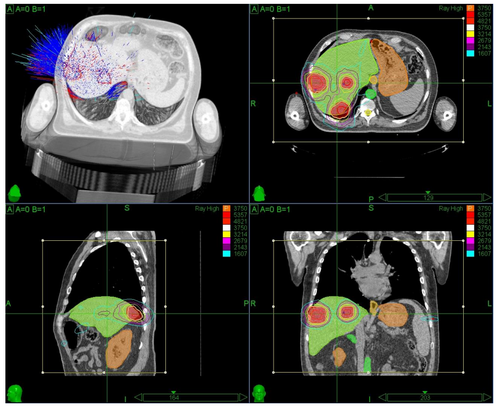
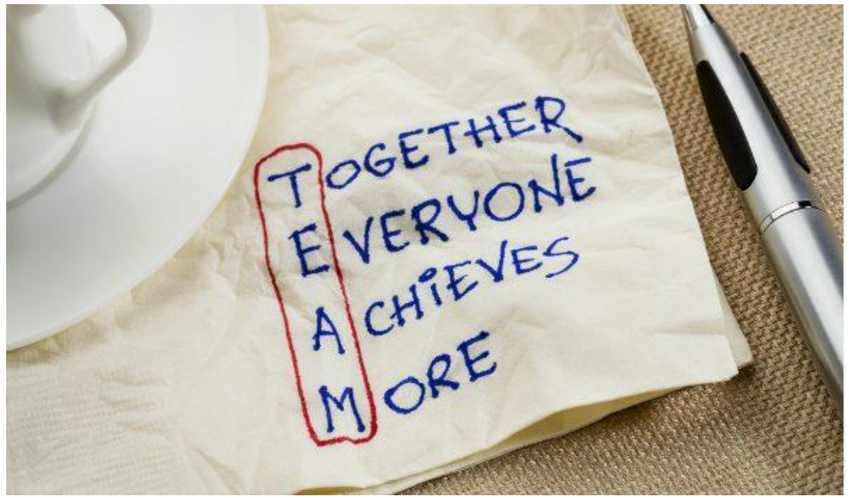
RT a fasci esterni



Paziente oligometastatico, per migliorare i risultati della terapia singola

Paziente in cui la dosimetria sulle lesioni tumorali mostri una captazione non tumoricida

Paziente con captazione mista (sedi captanti e sedi non captanti)



Grazie per l'attenzione…