Montpelier, 16 març 2022

SEMINAIRE DE RADIOTHERAPIE INTERNE VECTORISEE

Radiobiologie clinique

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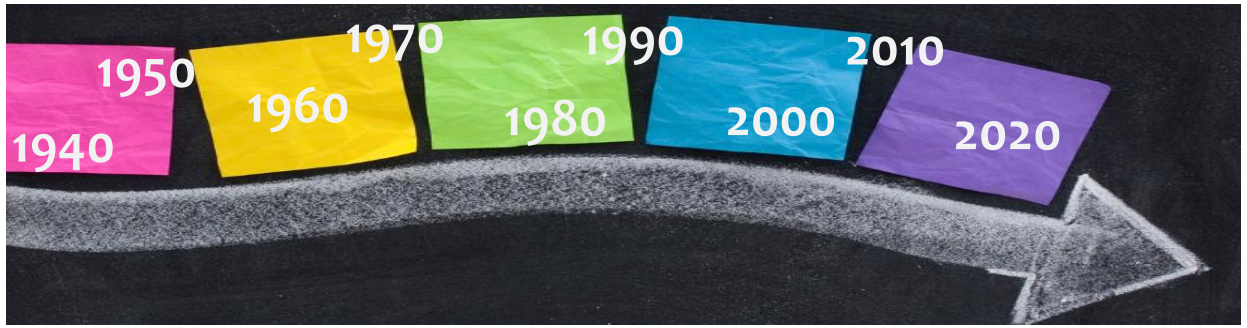
Radiothérapie Interne Vectorisée

Beaucoup d'applications

Peu de conaissances sur les effets radiobiologiques

Beaucoup à découvrir…

- ^{131}I: hyperthitoidism, differentiated thyroid cancer (DTC)
- ^{89}Sr, ^{153}Sm-EDTMP, ^{223}Ra-chloride: Bone Metastases
- ^{131}I-mIBG: pheocromocitomas, paragangliomas
- Radioimmunotherapy(RIT) (Zevalin, Bexxar): NHL
- Peptide Réceptor Radionuclide Therapie: Neuroendocrine Tumors
- SIRT/Radioembolization: Primary and Metastatic Liver Tumors …
- ^{177}Lu-PSMA



Quand a- t-on commecé à comprendre sérieusement

que la dose absorbée ne suffisait pas et qu'il fallait

introduire des models radiobiologiques

dans le domaine de la **RIV** ?

2003

^{166}Ho-DOTMP:
Premier cas de **toxicité rénale très sérieuse** à doses «plutot» faibles

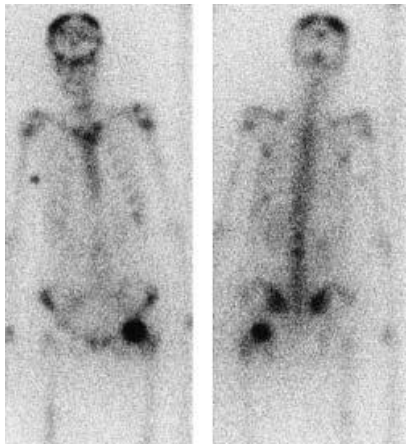
^{166}Ho-DOTMP utilizé pour l'irradiation de la moelle ossuse (au cible **25 Gy)** avant la transplantation de cellules staminaless en patients avec myeloma.

à la véssie (MIRD 14): **45-155 Gy**

aux reins (ICRP 53): **0.5-8 Gy**

→ **33% G1–G3 toxicité à la véssie**

35% G3-G4 toxicité rénale



460-4480 mCi
17-166 GBq

excretion rénale très rapide:

Durée de transite par les reins : 2.6 min

Les images à 3 h ne montrent pas (plus) de captation rénale

" severity was related to radiation dose and probably to **dose rate** "

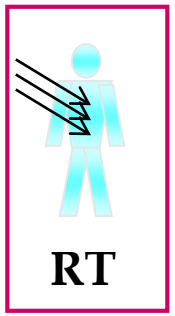
Breitz H et al. Ca Biother Radiopharm. 2003;18(2):225-30.

Modèle linéaire quadratique LQ

$$SF(D_t) = \exp(-\alpha D - \beta D^2)$$

BED - biological effective dose

α radiosensitivity β sparing capacity



External Beam Radiation Therapy

d = dose/fr

D = d · n fractions

(i.e. total treatment dose)

$$BED = n \cdot d \cdot \left(1 + \frac{d}{\alpha/\beta}\right)$$

Nuclear Medicine Therapy

repair half- life T_{rep}

effective half-life T_{eff}

$$BED = D + \frac{G(\infty)}{\alpha/\beta} D^2$$

Lea-Catcheside factor, inclding μ repair costant of DNA during the prolonged irradiation

α/β = **7-20** Gy / **0.5-6** Gy acutely / late responding tissues

Typically: α/β = **10 Gy** tumors; **3 Gy** normal organs

T_{rep} = **1.5 h / 0.5 h** repair half-life normal tissues / tumors

Barendsen, 1982;
Fowler, 1989; Bodey, 2003

Response to radiation may depend more on dose rate than dose

Kidneys are slowly proliferating cells (→ late responding). Low $\alpha/\beta \sim 2.4$ Gy.
RE is higher at high dose rates for slowly proliferating tissues (kidneys) than for rapidly proliferating tissue (tumor, bone marrow).

Despite low absorbed doses, dose rate effects could have provoked the toxicity

Relative Effectiveness of radiation

$$RE = 1 + \frac{R_0}{(\mu + \lambda e)(\alpha/\beta)}$$

R_0: initial dose rate
μ: tissue repair, λ_e: effective decay

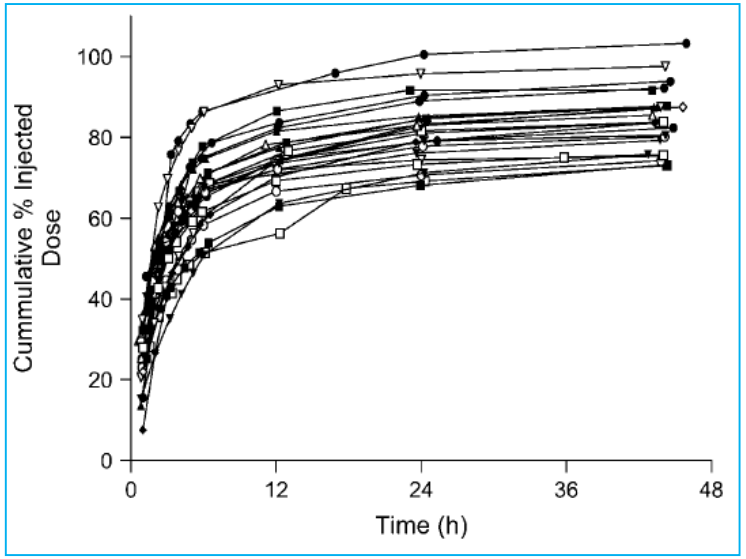
Dale, PMB 1996

2006

absorbed dose to the kidneys:

2-4 Gy ICRP 53, **8-17 Gy** imaging !

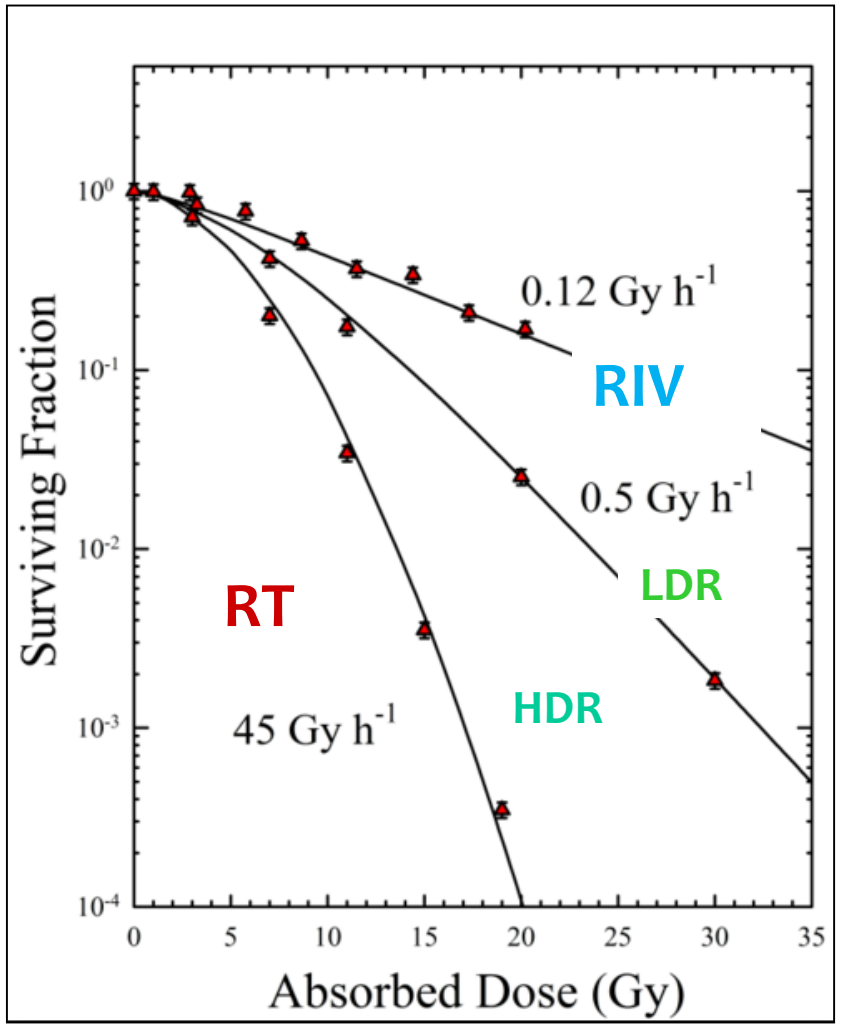
BED = 20 - 44 Gy



Initial dose-rate to the kidney: 0.7 Gy/h, with rapid decrease
If T_{rep} 1h, $\alpha/\beta = 2.4$ Gy RE = 1.3 (BED = 1.3·D = 10-22 Gy)

Breitz H et al. J Nucl Med. 2006;47(3):534-42.

éffet du débit dose



Le débit de dose influence beaucoup la réparation du dommage sub-létale

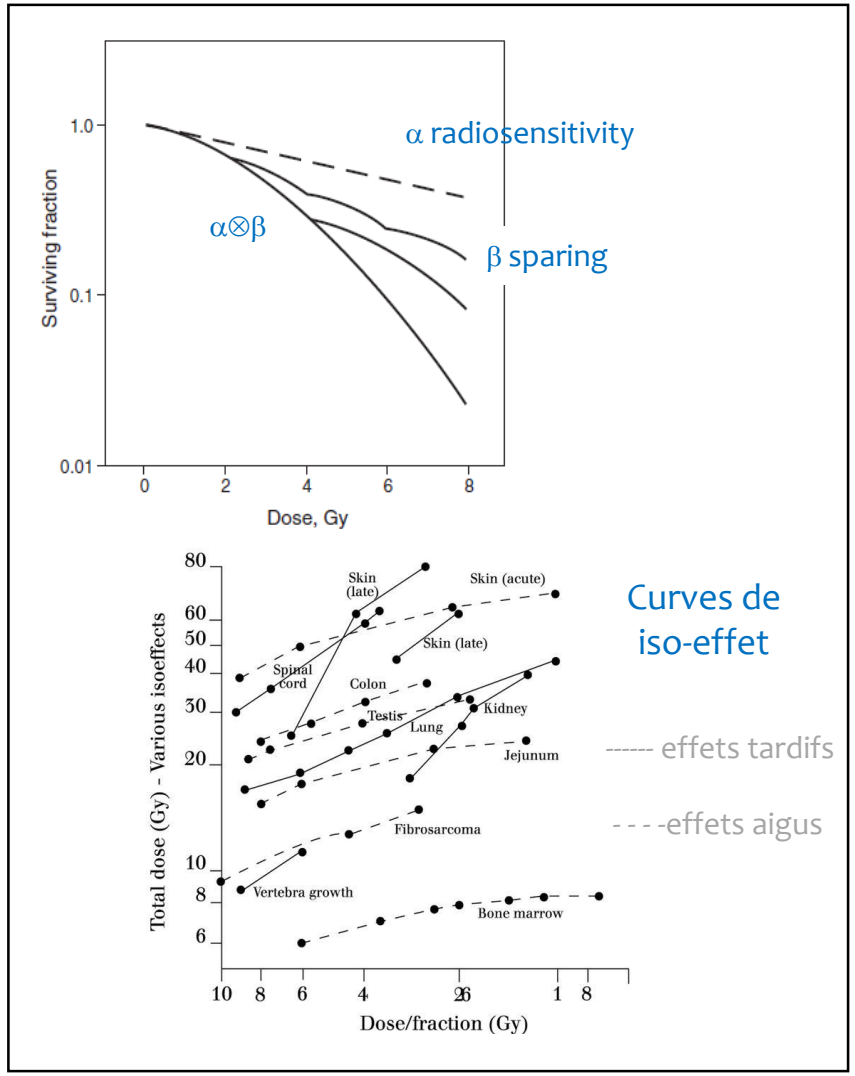
↓ dose-rate, ↓ β

le debit de dose a peu d'influence sur les tumours (ou les tissus à proliferation rapide)

le debit de dose influence beaucoup les tissus normaux (ou tumeurs à proliferation lente): ↓ d debit de dose, ↓ toxicité

↑ fractionément
↑ dose cumulative possible

effet du fractionnement



RIV = bas débit de dose; plusieurs cicles peuvent réduire la toxicité sans affecter la réponse

Quelques examples de RIV oú des concepts radiobiologiques:

- **ont été evidents** → *ont stimulé plusieurs études*
- **ont été considérés pour changer le protocol de la thérapie**

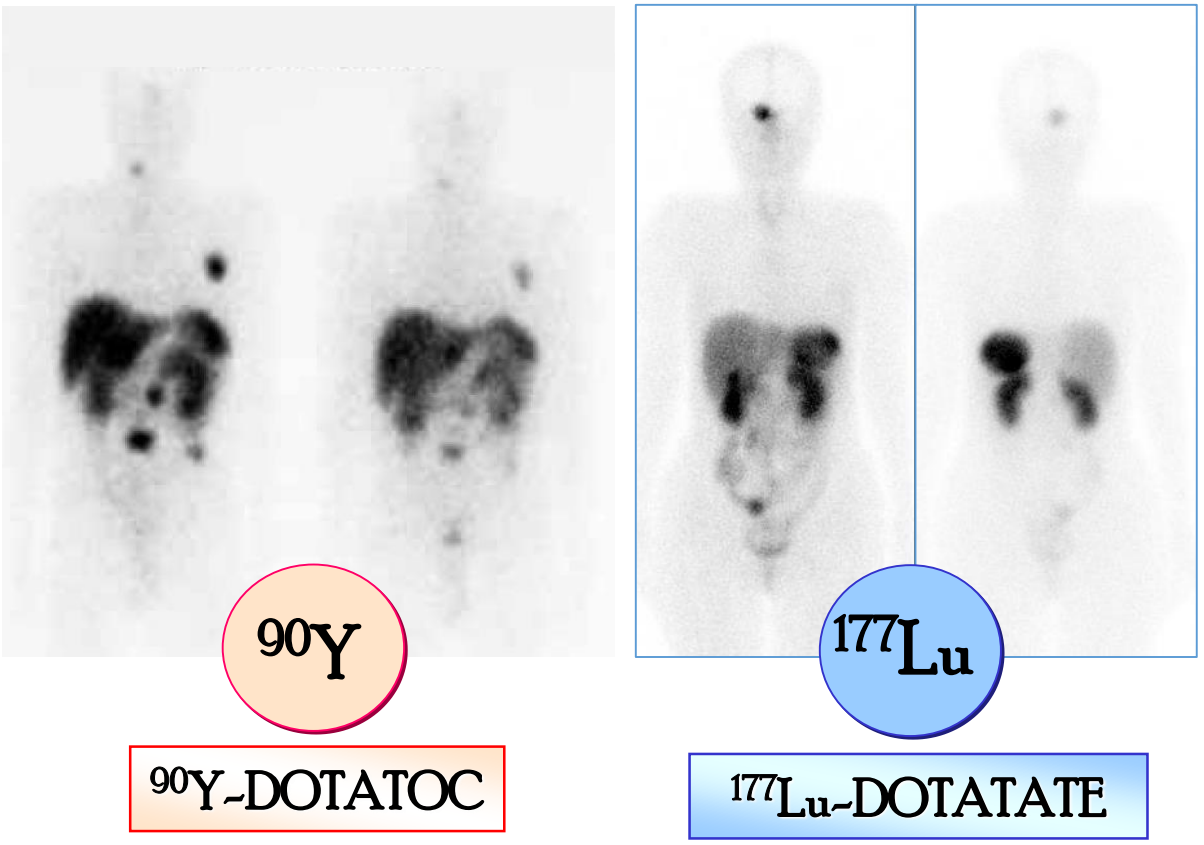
en ordre cronologique…

- **PRRT avec ^{90}Y e ^{177}Lu pour les NET**
  - **SIRT / Radioembolisations de lésions épatiques – ^{90}Y microsfères**
    - **Traitements successifs ou combinés de EBRT et RIV**

PRRT avec ^{90}Y et ^{177}Lu

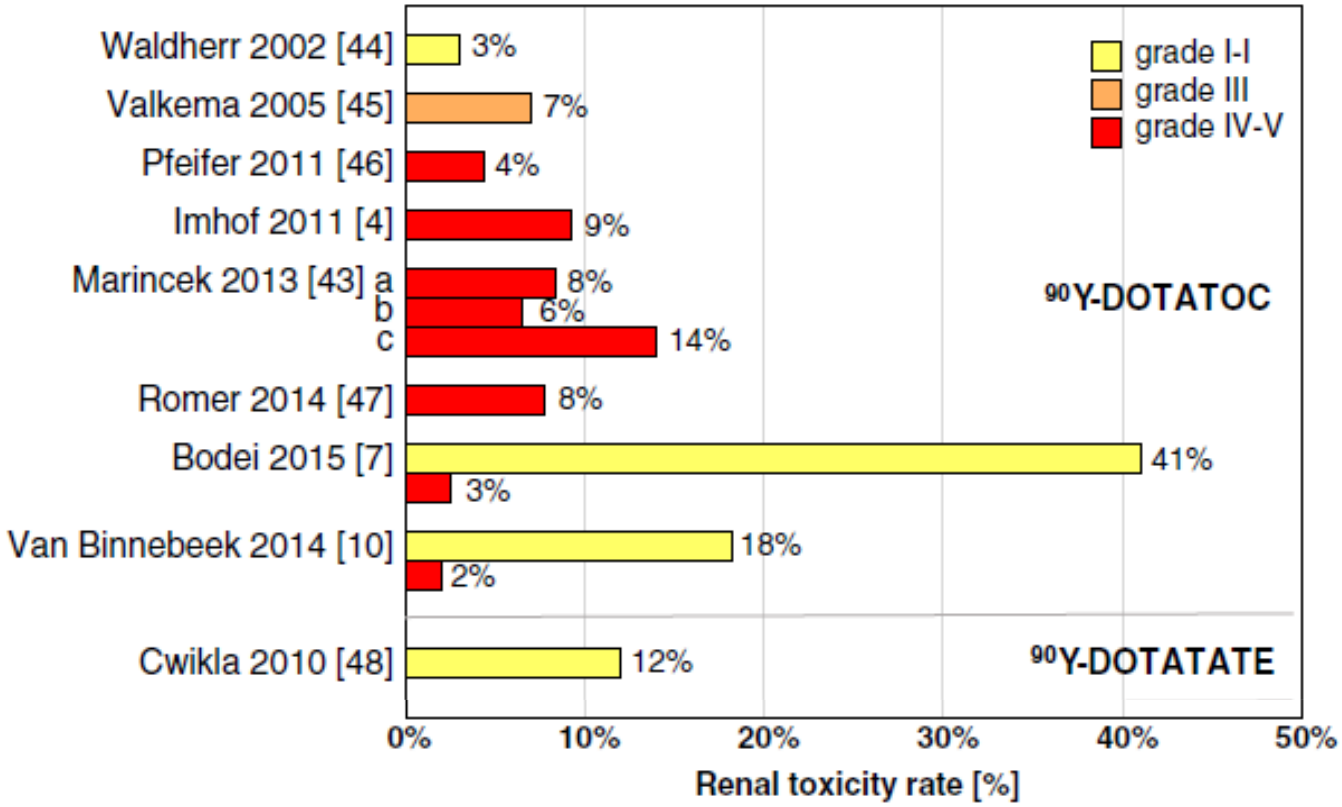
pour les tumeurs neuroendocrines (NET)

Peptide
Receptor
Radionuclide
Therapy



radiolabelled peptides able to bind to somatostatin receptors, for a selective irradiation of tumour cells

Renal toxicity has been observed in ^{90}Y-PRRT



in patients with long life expectancy

Impact of number of cycles – ^{90}YPRRT

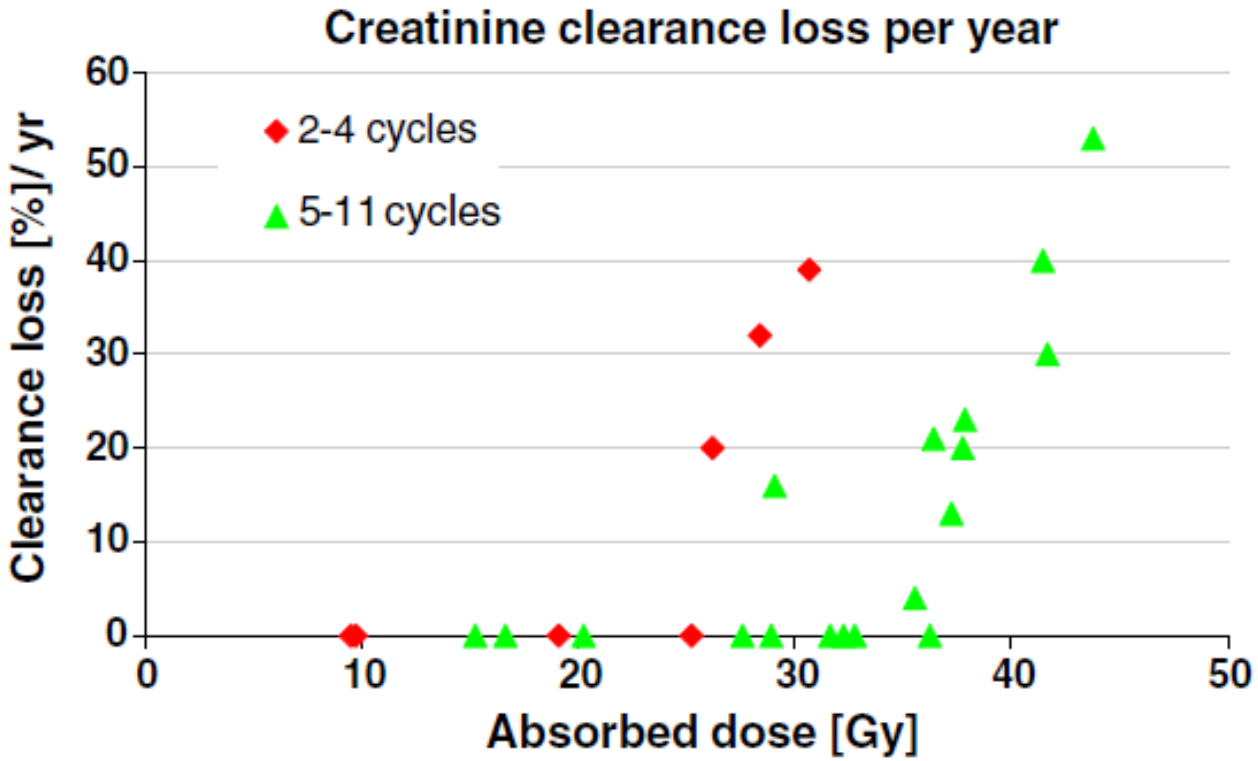


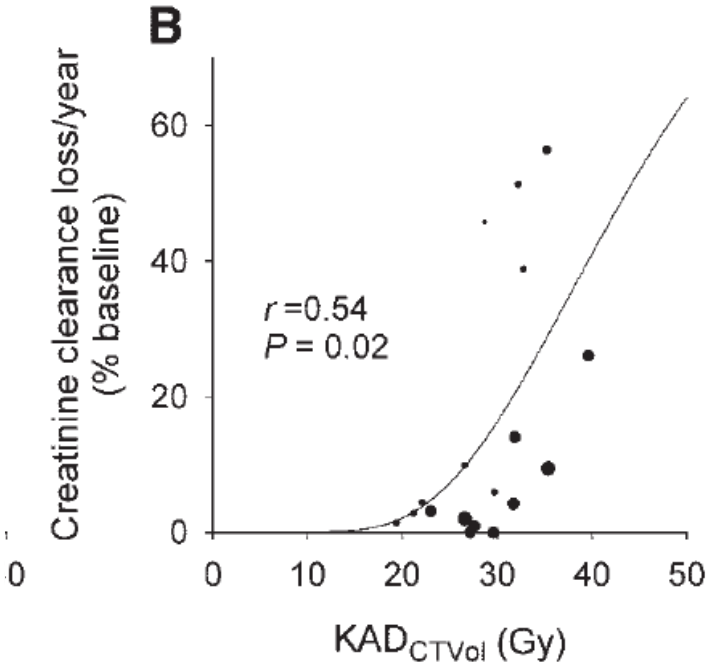
Fig. 4 Creatinine clearance loss as a function of cumulative absorbed dose to the kidneys for 2 to 4 cycles (*diamonds*) and 5 to 11 cycles (*triangles*). Patients receiving therapy in a higher number of cycles experienced creatinine clearance loss at higher absorbed doses. Data derived from the study by Bodei et al. [37]

^{90}Y-DOTATOC

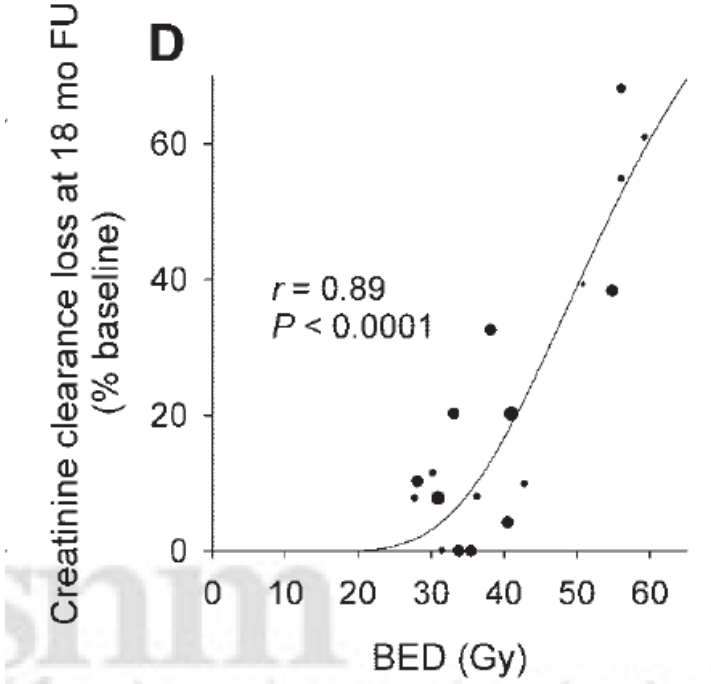
Patient-Specific Dosimetry in Predicting Renal Toxicity with ^{90}Y-DOTATOC: Relevance of Kidney Volume and Dose Rate in Finding a Dose–Effect Relationship

Raffaella Barone, MD[1]; Françoise Borson-Chazot, MD, PhD[1]; Roelf Valkema, MD, PhD[2]; Stéphan Walrand, PhD[1]

dose



BED



Barone R, et al.
JNM 2005;46 Suppl 1:99S-106S.

LQ model: equations for MN

Surviving-Fraction curves (SF%)

$$SF = \exp(-\alpha\, BED)$$

or, to highlight the variation of dose vs. time (D_t):

$$SF(D_t) = \exp(-\alpha D_t - g(t)\cdot\beta\cdot D^2_t)$$

$g(t) = A\,[1-E_t+F_t]/H_t$

$A=\lambda_e/(\lambda_e+\mu)$; $E_t=2\cdot\lambda_e/(\lambda_e-\mu)\cdot\exp(-(\lambda_e+\mu)\cdot t)$;

$F_t=(\lambda_e+\mu)/(\lambda_e-\mu)\cdot\exp(-2\lambda_e\cdot t)$; $H_t=(1-\exp(-\lambda_e\cdot t)^2)$

Biological-Effective-Doses (BED) for MN

Organs

$$BED_i = D_i + \beta/\alpha \cdot \frac{T_{1/2rep}}{T_{1/2rep}+T_{1/2eff}} \cdot D_i^2$$

dose-rate 1-exp, riparazione danno subletale 1-exp, irradiazione prolungata

Tumours (including repopulation)

$$BED = D + \beta/\alpha \cdot \frac{T_{1/2rep}}{T_{1/2rep}+T_{1/2eff}} \cdot D^2 - \ln 2 \cdot \frac{\Delta T}{\alpha \cdot T_{av}}$$

wasted dose

radiobiological parameters

Kidneys	
T_{repair}	2 h
α/β	2.5 Gy
α_{cortex}	0.06 Gy^{-1}

Tumours	
T_{repair}	0.5-1.5 h
T_{av}	10, 30, 60 days
α/β	10 Gy
α_{tum}	0.3 Gy^{-1}

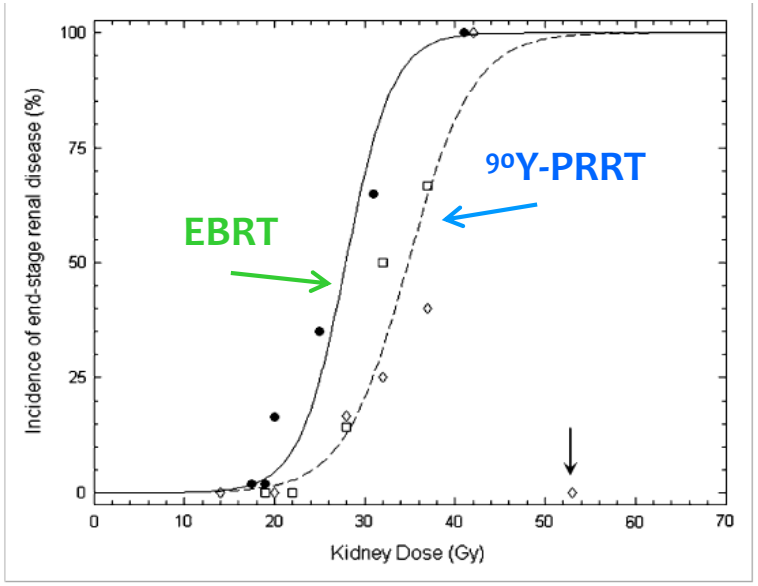
→ *clonogenic doubling time*

démie vie effective

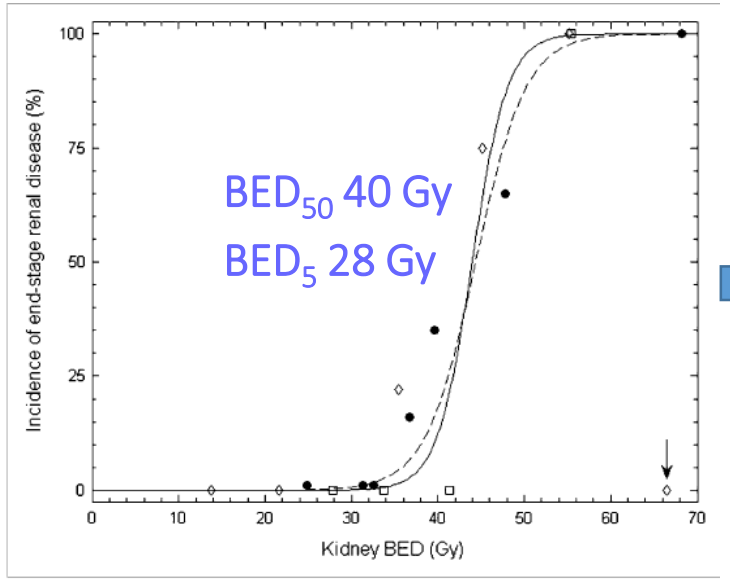
Bouchet et al. MIRD19 JNM 2003 1113-47 Dale Phys Med Biol 1996 1871-84. Wessels et al. MIRD20 JNM2008 1884-99

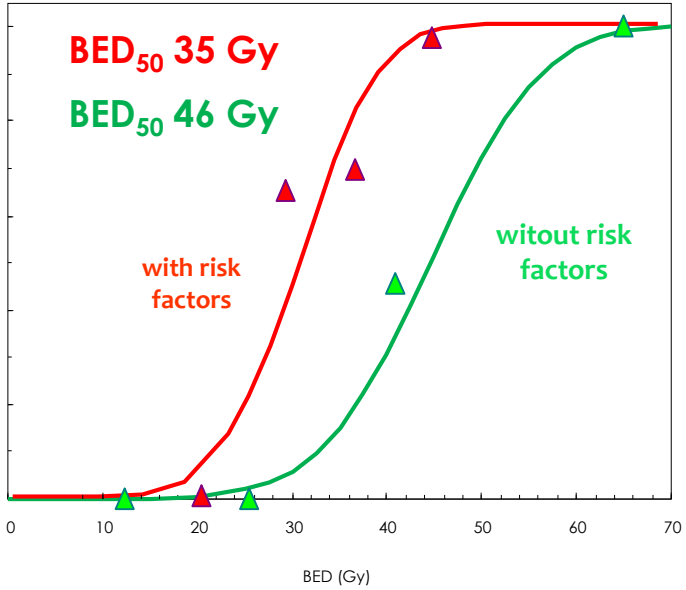
dose effect correlations for kidneys exist for ^{90}Y-PRRT

Absorbed dose vs. renal toxicity



BED (Biological Effective Dose)





Patients can be stratified!

Extrapolation to ^{177}Lu ?

démie vie effective

D_{50} Lu 36 Gy

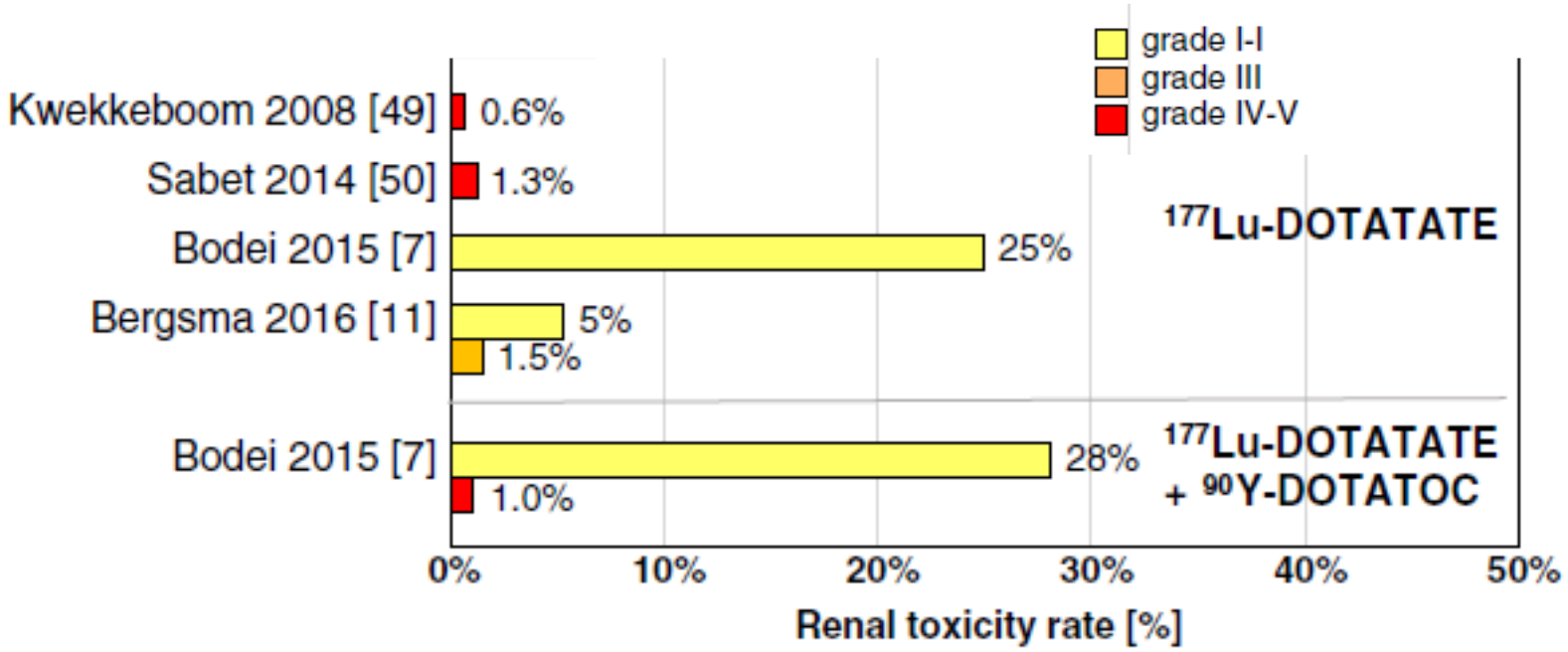
D_5 Lu 26 Gy

is it that simple?

This applies in the hypothesis of
dose uniformity, which is it not the case

Wessels et al, JNM, 2008

Severe renal toxicity is not observed in ^{177}Lu-PRRT



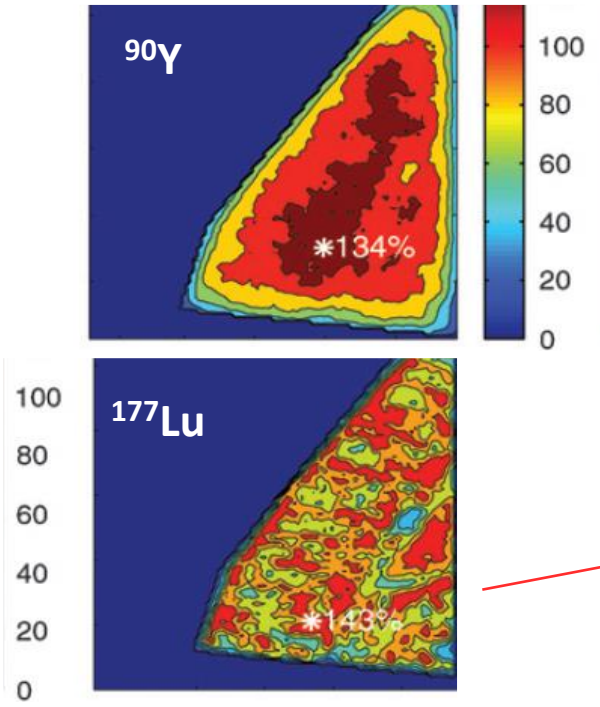
no grade III /IV of nephropathy, only some cases of grade I is reported by some authors

no NTCP correlation curves are derivable

dose uniformity in renal cortex

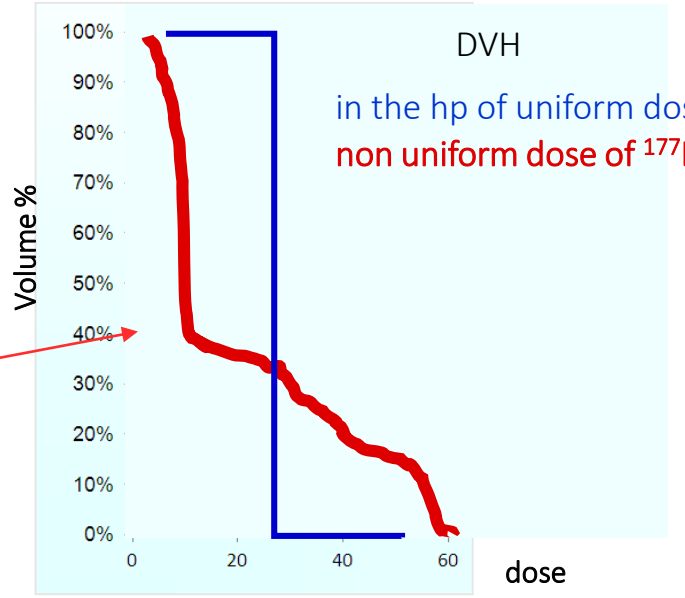
what do dosimetric models indicate

Dose distribution in renal cortex from autoradiography



Konijnenmerg M et al, JNM 2007

The hp of uniform dose is almost acceptable for ^{90}Y but not for ^{177}Lu



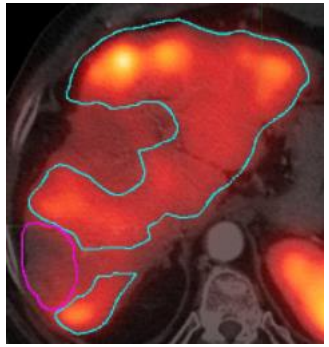
much less volume receives high doses

less damage
for a same mean dose

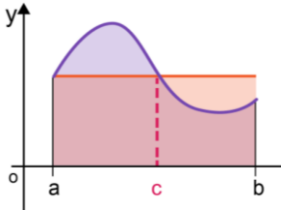
The higer non-uniformity of ^{177}Lu should mitigate the renal burden as compared to ^{90}Y
→ **higher tolerability of ^{177}Lu** as compared to "mean dose" from hp of uniformity

matching with what is clinically observed

several dosimetric parameters can be considered



AD Mean absorbed dose

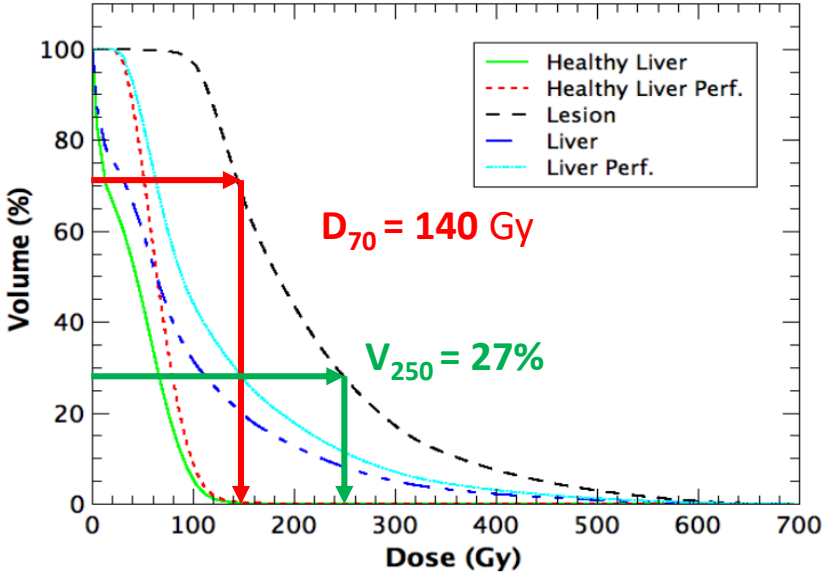


Voxel dosimetry

DVH Dose volume hystogram

D_{70} … minimum dose to 70% of the volume

V_{250} … % of the volume receiving at least 250 Gy



EUD

$$\mathrm{EUD} = \left(\sum_i D_i^{\frac{1}{n}} v_i \right)^n$$

Equivalent Absorbed Dose

BED

$$\mathrm{BED} = D_T + D_T^2 \frac{\lambda}{(\mu + \lambda)} \frac{1}{\alpha/\beta}$$

Biological Equivalent Dose

$$\mathrm{SF}(D) = e^{\left(-\alpha D - g(T)\cdot\beta D^2\right)}$$

EUBED

$$= -\frac{1}{\alpha}\left[\ln \sum_i^M \frac{\mathrm{SF}_i}{N} \right] = -\frac{1}{\alpha}\left[\ln \sum_i^N \frac{\exp(-\alpha \cdot \mathrm{BED}_i)}{N} \right]$$

$$\mathrm{EUBED} = \mathrm{EUD} + \frac{1}{\alpha/\beta} \frac{T_{rep}}{T_{rep} + T_{eff}} \mathrm{EUD}^2$$

α/β = 3 Gy -> 10 Gy normal -> tumor tissues
μ= repair constant of sublethal damage

Amato E, et al. Journal of Physics 2020

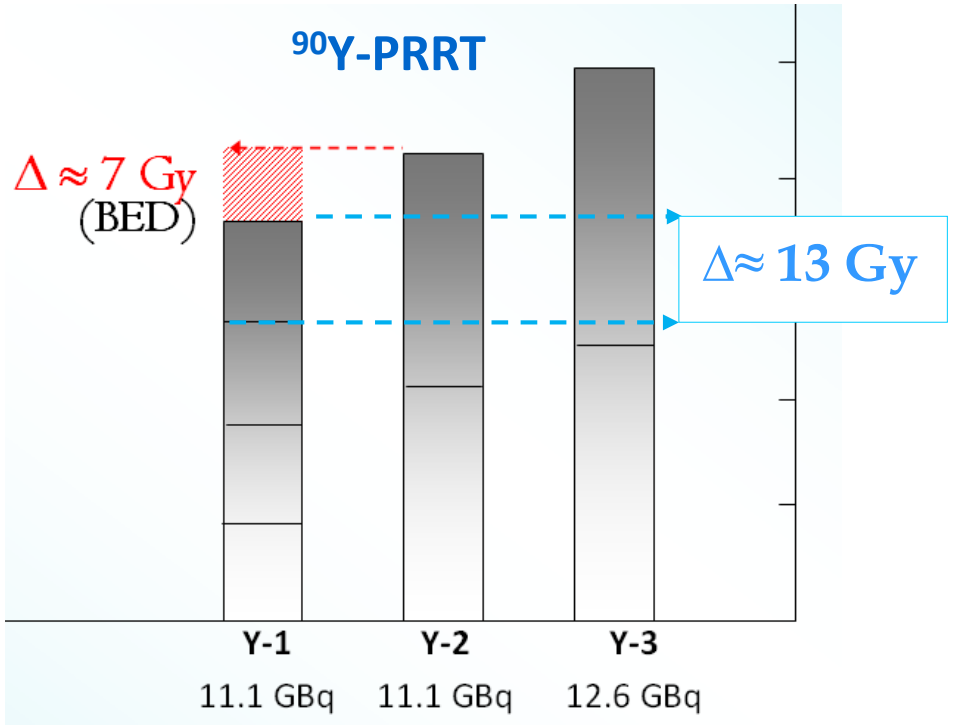
Therapeutic schemes in ^{177}Lu and ^{90}Y-PRRT: radiobiological considerations

Anna SARNELLI [1] *, Francesco GUERRIERO [2], Francesca BOTTA [2], Mahila FERRARI [2], Lidia STRIGARI [3], Lisa BODEI [4], Vincenzo D'ERRICO [1], Elisa GRASSI [5], Federica FIORONI [5], Giovanni PAGANELLI [6], Roberto ORECCHIA [7-9], Marta CREMONESI [2]

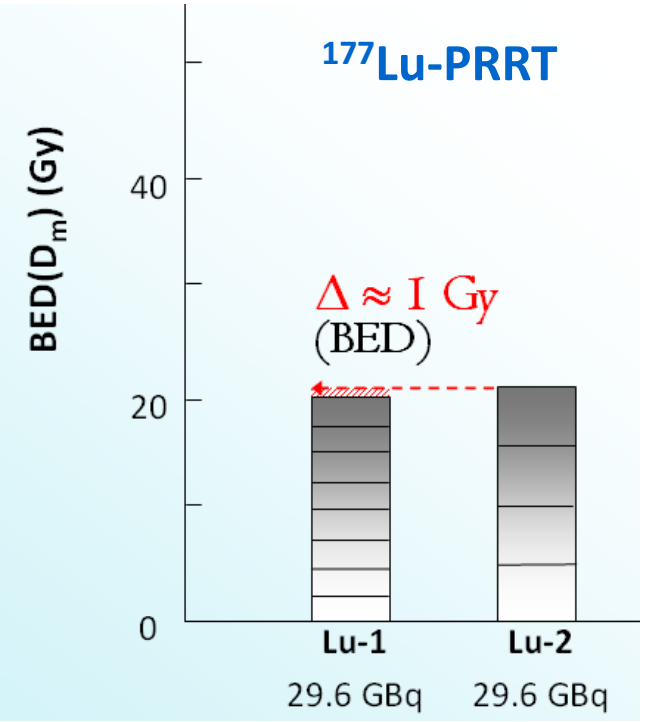
Sarnelli A, et al. Q J Nucl Med Mol Imaging. 2017;61(2):216-231.

the impact of cycles in ^{90}Y and ^{177}Lu

while for ^{90}Y, and higher absorbed doses, the **impact of cycles is quite relevant**: more cycles increase tolerability



for ^{177}Lu, and lower absorbed doses, the **impact of cycles is negligible**



Modèle extrapolé pour les reins

Sarnelli A, et al. Q J Nucl Med Mol Imaging. 2017;61(2):216-231.

Wessels B, et al 2008: FSU = Fractional Sub Unit ; SF_{FSU} 25% limite pout l'insuffisance rénale

PRRT schemes	Activity distribution	SF_{FSU} (kidney) comparison in PRRT by LQ model			
		CORTEX			WHOLE KIDNEY
		EUBED/BED	SF_{FSU}% (D_{mK})	SF_{FSU}% (EUBED)	SF_{FSU}% (D_{mK})
Lu-1 30 GBq, 4-8 cy	Unif	**0.95**	**43**	**34**	**32**
	Non-unif	**0.51**		**56**	
Y-90 11 GBq, 4 cy	Unif	**0.89**	**23**	**17**	**14**
	Non-unif	**0.62**		**29**	
Y-90 11 GBq, 2 cy	Unif	**0.86**	**18**	**14**	**10**
	Non-unif	**0.59**		**26**	
Y-90 13 GBq, 2 cy	Unif	**0.82**	**13**	**11**	**7**
	Non-unif	**0.57**		**22**	

À parité de dose moyenne cumulative

À parité (presque) de dose moyenne cumulative

…stimulant la recherche en radiobiologié

' SF_{FSU} ' = 'Fonctionalité' de la FSU *

^{177}Lu-PRRT basée sur la dosimétrie pour augmenter l'éfficacitée

Individualized Dosimetry of Kidney and Bone Marrow in Patients Undergoing ^{177}Lu-DOTA-Octreotate Treatment

Sandstrom M et al. J Nucl Med 2013; 54:33–41

Hp: plus de cycles, fixée dose aux reins
plus grand effet sur les tumeurs

200 pts, 7.4 GBq/cy

Dose < 23 Gy to kidneys or 2 Gy to RM

limiting organ: kidney (197/200 pts)

- In **50%** of pts, **more than 4 x 7.4 GBq** could be administered
- **up to 10 cycles**
- fewer than 4 cycles in 20% of pts

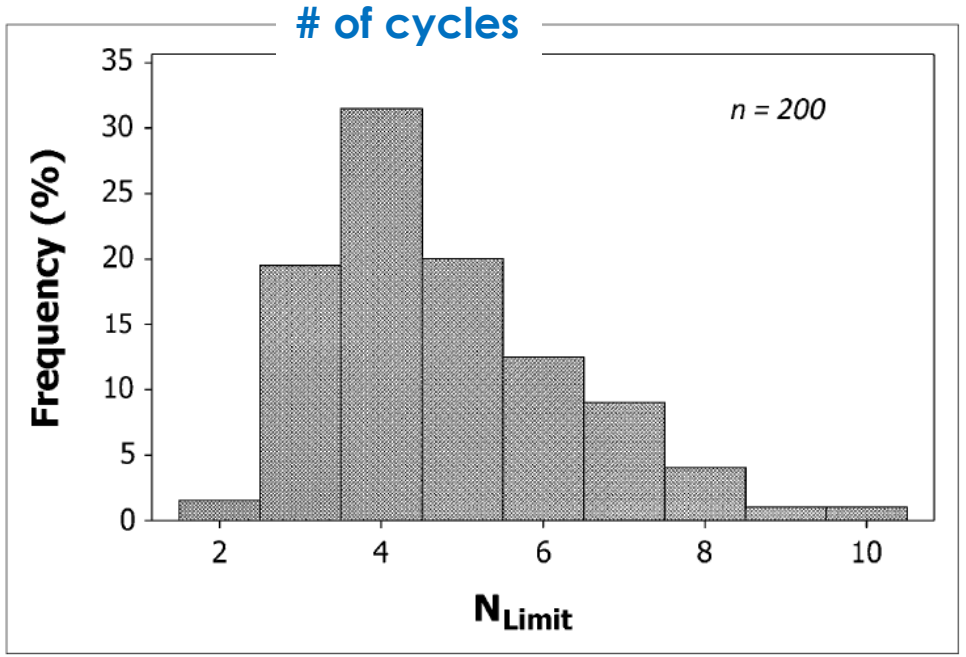
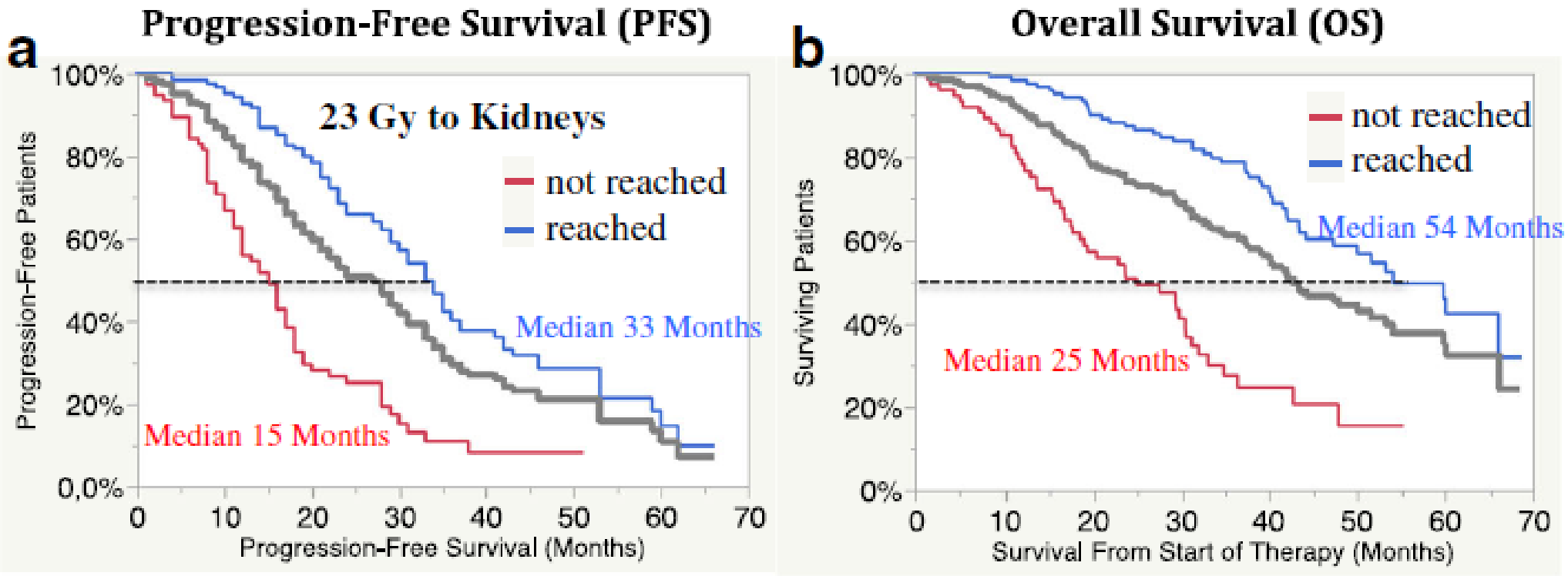


FIGURE 7. Maximum tolerable number of cycles with respect to absorbed doses to bone marrow and kidneys for 200 patients.

Clinical outcome based on a dosimetry - ^{177}Lu-PRRT

Treatment planning: **n. of cycles of 7.4 GBq** up to reach **23 Gy to kidneys**



Pts with absorbed dose to the **kidneys 23 Gy → higher total activity in most patients → higher OS**
Pts with **CR/PR → higher OS** vs. patients with SD

Consistent advantage of personalized treatement !

Garske-Román U, EJNMMI 2018

Eur J Nucl Med Mol Imaging (2017) 44:1490–1500

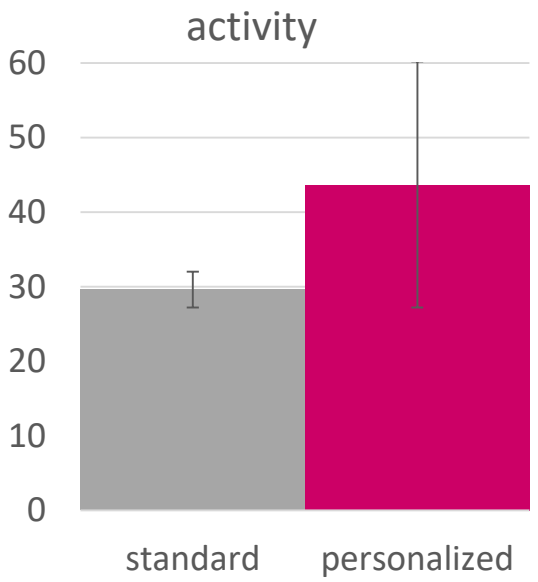
Personalized ^{177}Lu-octreotate peptide receptor radionuclide therapy of neuroendocrine tumours: a simulation study

Michela Del Prete[1,2] · François-Alexandre Buteau[1,2] · Jean-Mathieu Beauregard[1,2]

4 cycle protocol based on dosimetry

prescribed renal absorbed dose: 23 Gy in 4 cy

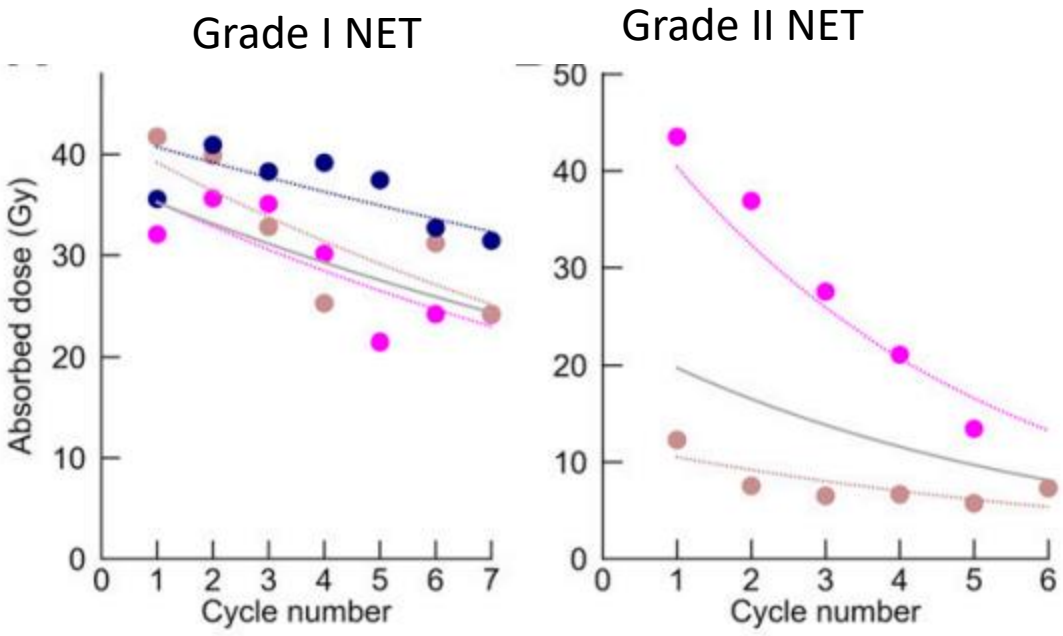
44 ± 17 **GBq ~ 1.5-fold increase of activity**
vs. standard 30 GBq in 4 cy



Kidney 22 ± 3 Gy
RM: 1.6 ± 0.6 Gy
tumor 165 ± 85 Gy

significant increase of tumor absorbed dose, to increase the therapeutic benefit while limiting toxicity

Tumour Dose variation with cycles



Roth D, et al. J Nucl Med 2022;63(3):399-405.

Térapies combinées: EBRT et RIV:

combination treatmenti is a hallmark of cancer therapy, Hobbs JNM 2013

rationale

- ✓ **to increase efficacy**
- ✓ **to includere lesions not alwyas visible (advantage of a systemic therapy)**
- ✓ **higher tolerabiliy (different OARs in PRT and EBRT)**
- ✓ **managment of a patient needing PRRT after EBRT** (or viceversa)

anomalous case, EBRT after PRRT – worts dosimetry scenario

Pancreatic NET

^{177}Lu-PRRT

27.9 GBq

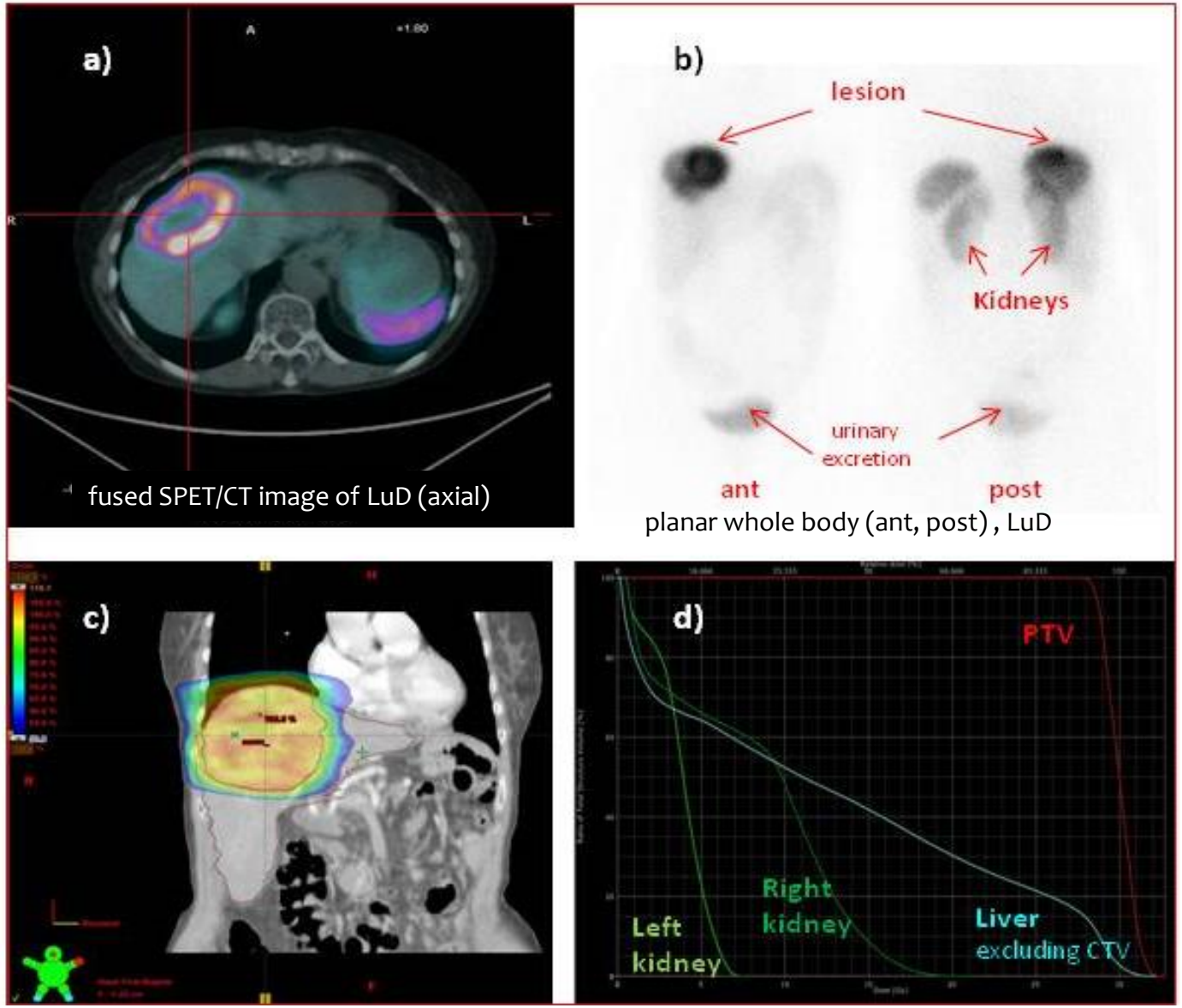
Liver met

(200 ml)

not responding to PRRT

EBRT prescribed, but

Kidenys (OARs of PRRT) are involved in EBRT irradiation



fused SPET/CT image of LuD (axial)

planar whole body (ant, post) , LuD

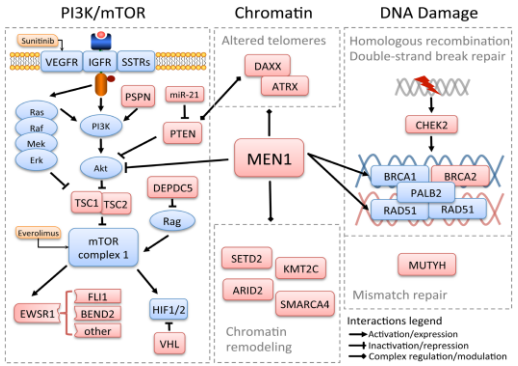
isodose distribution in a coronal plan

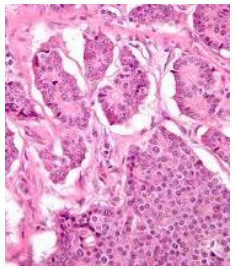
DVHs for the target and OARs. (PTV : planning target volume.

Clearly, dosimetry IS NOT the UNIQUE predictive parameter (cannot be)

but an essential piece of information, as well as

Tumor tissue characteristics





Ki-67

hystology

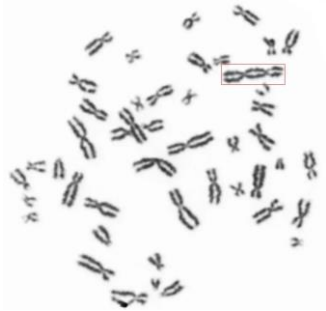
clinical hystory

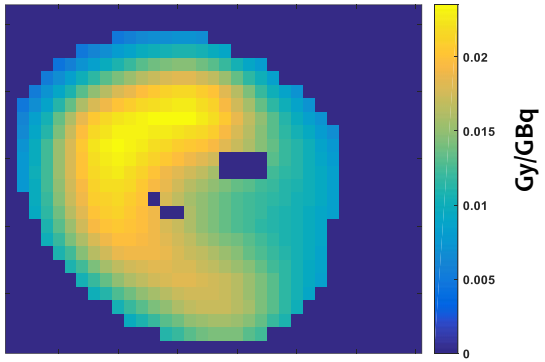
clinical parameters

radiobiology / radiosensitivity

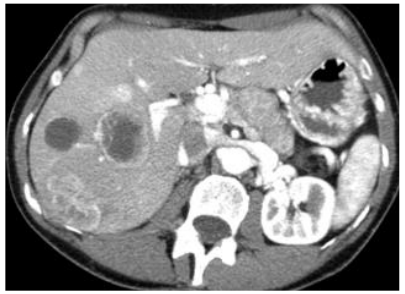
genetics

radiomics?....

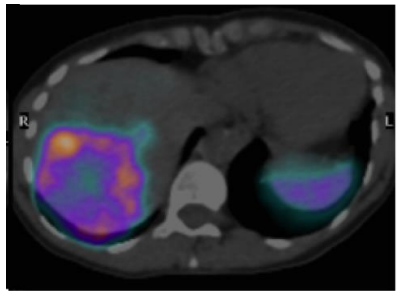




imaging

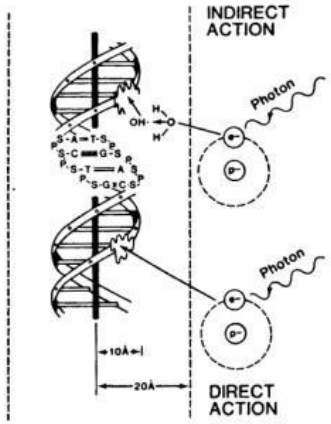


CT

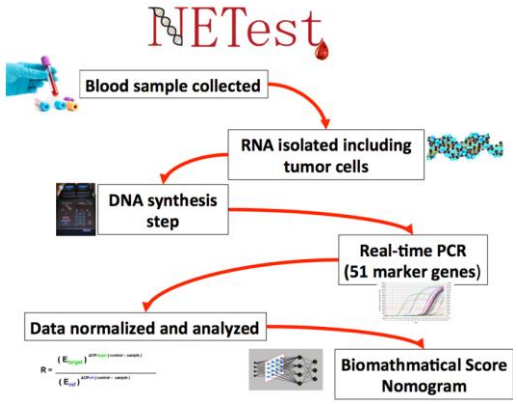


^{68}Ga-DOTATOC-PET/CT

^{18}FDG-PET/CT



Liquid biopsy



Résumé - 1

- **L'avantage Clinique** que la **dosimétrie** apporte à la RIV est de plus en plus evidente

  La dosimétrie n'est pas le seul paramètre predictif mais elle représente une **pièce cruciale de la radiobiologie**; il faut la combiner avec la biologie, le profil génétique, les dates cliniques pour dériver des modèles plus ciblés

- Donc, il est évident que pour entrer dans les trials prospectifs et améliorer les protocols, la **dosimétrie a besoin du support des modèles radiobiologiques**

- L'étude des **effets RB** sont à la base del la **personalization de la RIV**, pour bien sélectionner les patients, **éviter** la **toxicité** et les **sous-traitements**

Résumé - 2

- **Les models RB extrapolés de la EBRT et adaptés à la RIV** ont été capables de donner une **première interprétation** des effets (inhomogeneité, cycle), et des **corrélations dose-effets enrichissantes**

  Ils sont utiles aussi dans les cas de traitements combinés de RIV et RT

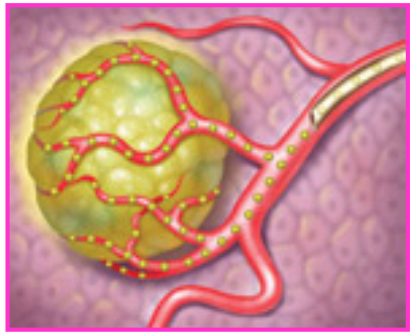
- Ces modèles peuvent représenter **une référence initielle**, mais ils faut les approfondir ou dévélopper des **models spécifiquement adressés** aux différentes applications, radionucléides (beta, alpha…)

- La recherche **radiobiologique pré-clinique** est très importante

merci beaucoup

marta.cremonesi@ieo.it

SIRT – Radioembolization des lésions du foie



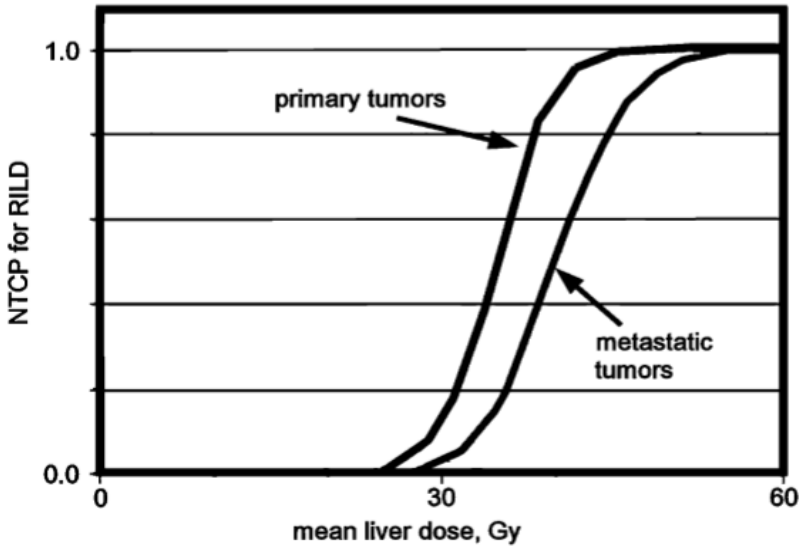
Traitement locorégionale

locoregional treatment with (90Y) microspheres injected into the hepatic artery. Microspheres are able to release high radiation doses to malignant hepatic lesions: **HCC** or liver **metastases**

- liver mainly supplied from the portal vein; tumours mainly supplied from hepatic artery (80-100%)
- tumours are passively targeted, microspheres are trapped in the arterioles within the tumour

- **HCC**
- **Métastases épatiques**
- **^{90}Y microsfères en verre**
- **^{90}Y microsfères en résine**
- **…**

EBRT:



Pan CC, et al. Radiation-associated liver injury. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S94-100

Table 1 | Characteristics of ^{90}Y-microspheres (6, 20, 24).

Commercial name	SIR-Spheres®	TheraSphere®
Manufacturer	Sirtex Medical, Lane Cove Australia	Therasphere BTG, Ontario, Canada
Material	Resin	Glass
^{90}Y sphere production	Bound to resin, attached to sphere surface	Embedded in a glass matrix
Particle size (μm)	32.5 ± 2.5 (range: 20–60)	25 ± 5 (range: 20–30)
Activity per sphere (Bq)	50 (range: 40–80)	2500 at the reference time
Number of spheres per GBq (million)	20 (mean)	0.4 at the reference time
Shelf-life	1 day	12 days
Specific gravity	Low (1.6 g/cc)	High (3.6 g/cc)
Embolic effect	Moderate	Mild
Activity available (GBq)	3	From 3 to 20, with step 0.5
Number of spheres in 3GBq	40–80 million	1.2 million at the time of calibration
Approved for	USA: HCC; Outside USA (especially Europe and Australia): unresectable liver tumors (HCC and metastases)	USA: colorectal carcinoma Outside USA (especially Europe and Australia): HCC and metastases
Handling for dispensing	Required	Not possible
Splitting one vial for two or more administrations	Possible	Not possible
Necessity of contrast medium guidance during administration	Yes	No

Tipiquement:

α/β 2.5 Gy foie, 10 Gy tumeur; T_{rep} 2.5 h foie, 1.5 h tumeur

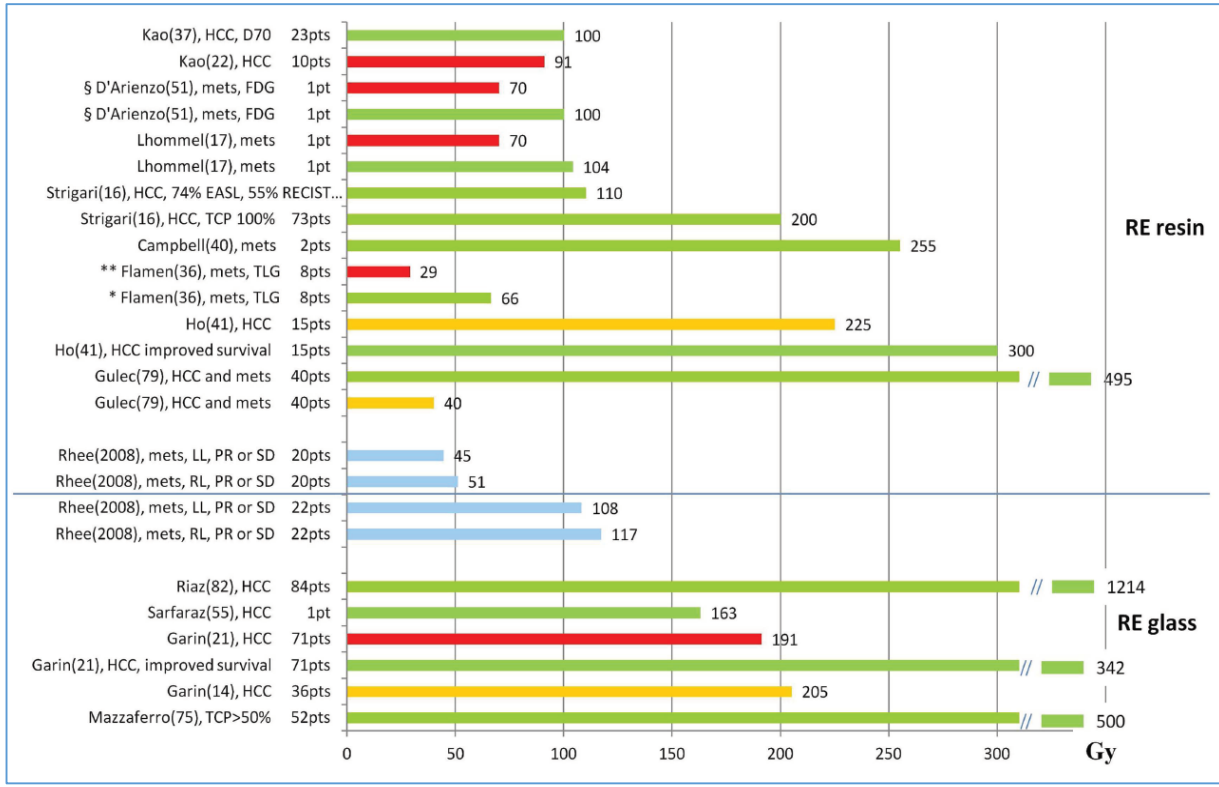
Cremonesi et al 2014

Prémières observations: pourquoi ?

Toxicité épatique vs. dose absorbée au foie

toxicité fatale; limite recommandée par l'auteur ou de toxicitée observée; traitement bien toléré

Réponse vs. dose absorbée à la tumeur

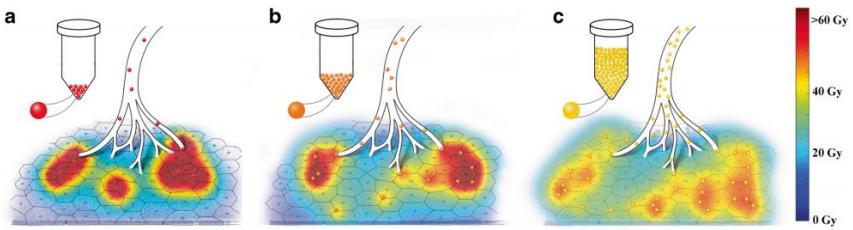


réponse (PR e CR), Stabilitée (SD), pirement (PD)

Cremonesi et al. Front Oncol. 2014 Aug 19;4:210. Review.

Evidences derived up to date

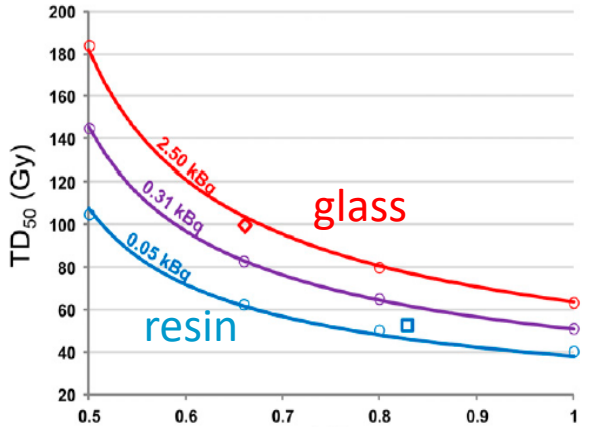
Activity (dose) distribution is not uniform
(micro- and or macroscopically)



Pasciak AS, EJNMMI 2020

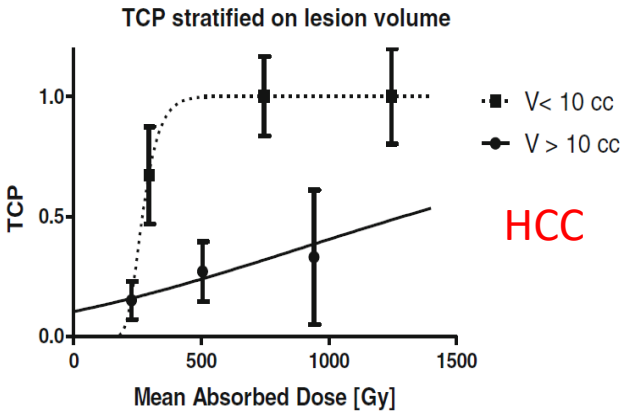
Resin vs. glass spheres / ≠ number of spheres
→ ≠ thresholds for response & toxicity

Högberg EJNMMI Res. 2014; Van der Gucht, JNM 2017; Walrand, JNM 2014

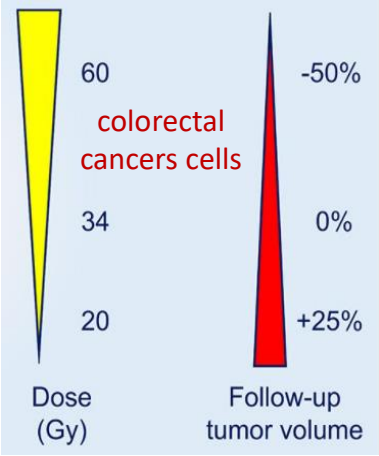


Volume fraction of normal Liver treated

Tumor response is correlated to absorbed dose

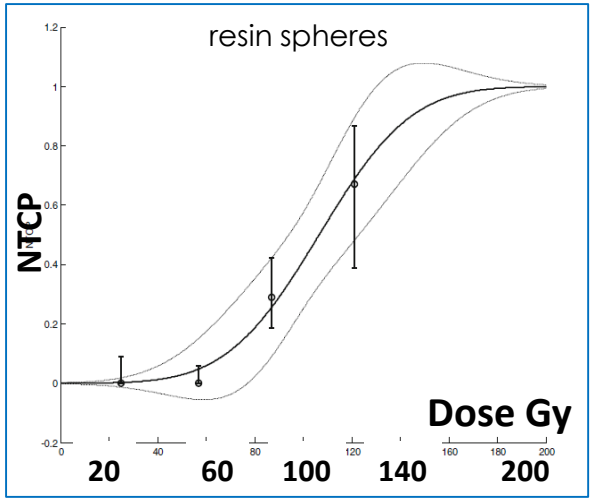


Chiesa C, EJNMMI 2015



Abbott EM, JNM 2020

The mean non tumoral WHOLE liver dose *NTWLD* is a prognostic factor for toxicity



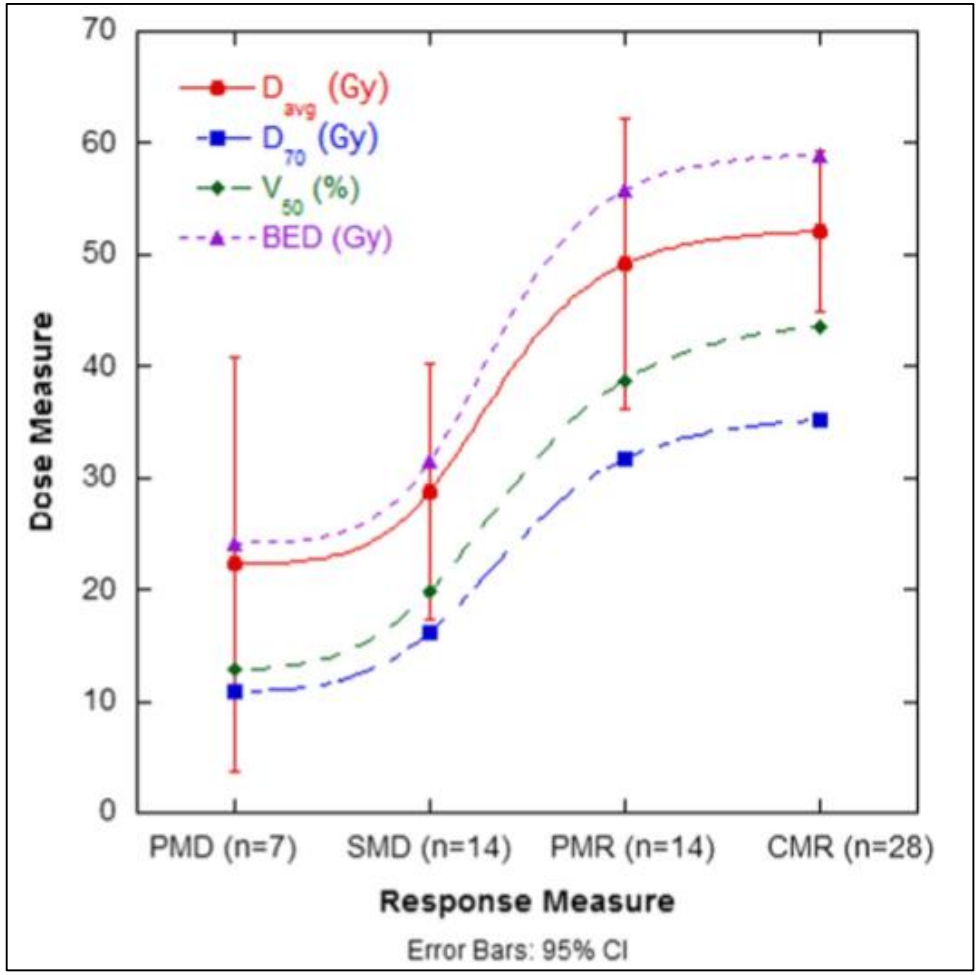
→ dose thresholds for toxicity with segmental, lobar or whole liver do differ
→ Separated in models

RE: 40 Gy well tolerated (resin)
75 Gy → 15% of toxicity (HCC)
EBRT: $TD_{50\%}$ = 30 Gy

Strigari, JNM 2010; Chiesa C, EJNMMI 2015

Willowson KP, et a. EJNMMI Res. 2017; 7(1):46

Clinical and imaging-based prognostic factors in radioembolisation of liver metastases from colorectal cancer: a retrospective exploratory analysis.



22 pts, 63 lesions

D_{mean} D_{70} V_{50} BED

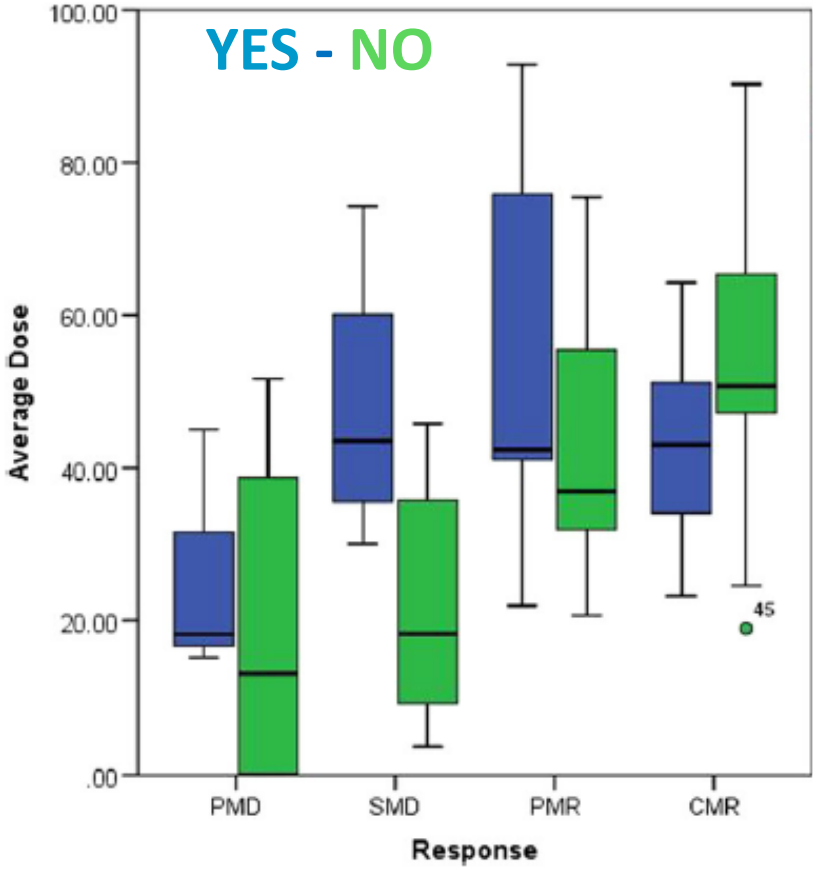
Responses at

D_{mean} > 50 Gy

for D<50 Gy, dose inhomogeneity has major influence on response

Clinical influent factors:
liver disease extension, genetic status, extrahepatic disease (OS)

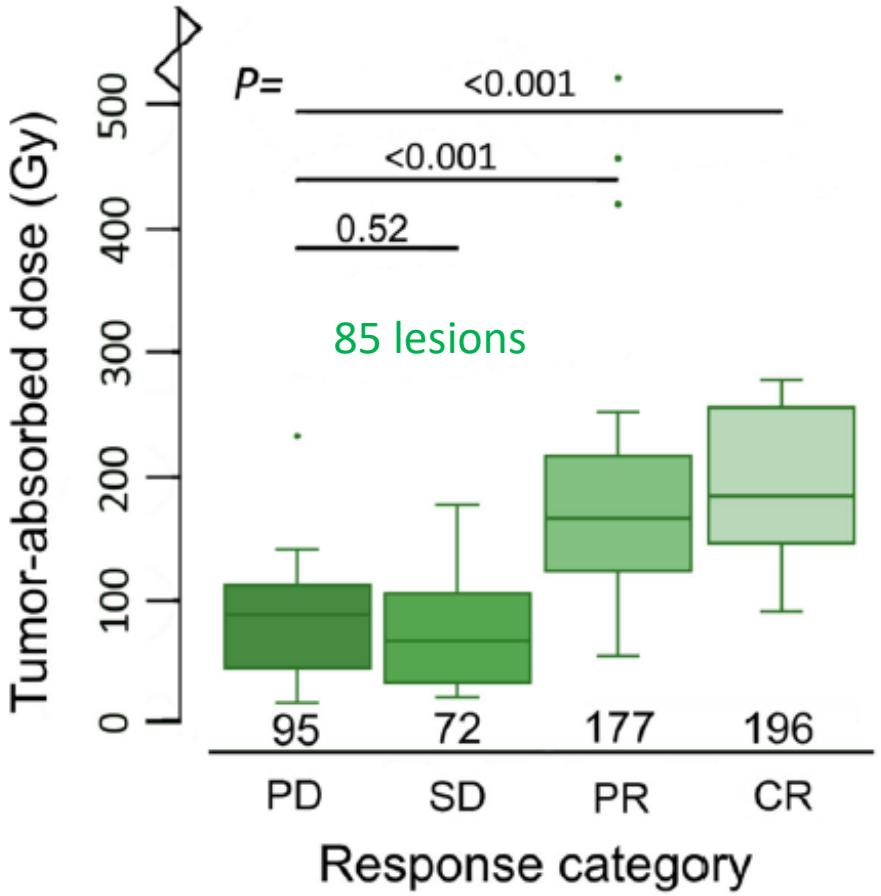
gene RAS mutation status

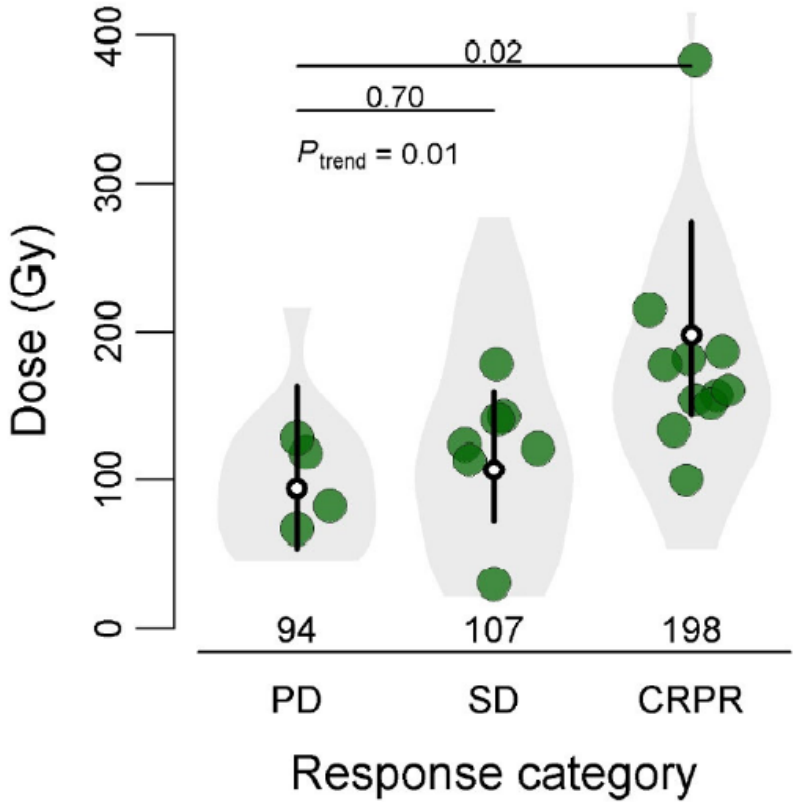


Alsultan AA, JNM 2021 *Mar. ahead of print*

Dose-response and dose-toxicity relationships for yttrium-90 glass radioembolization in patients with colorectal cancer liver metastases.

Metabolic response category @ 3 mo at tumor (L) and patient level (R)





31 pts, mean tumor dose per patient

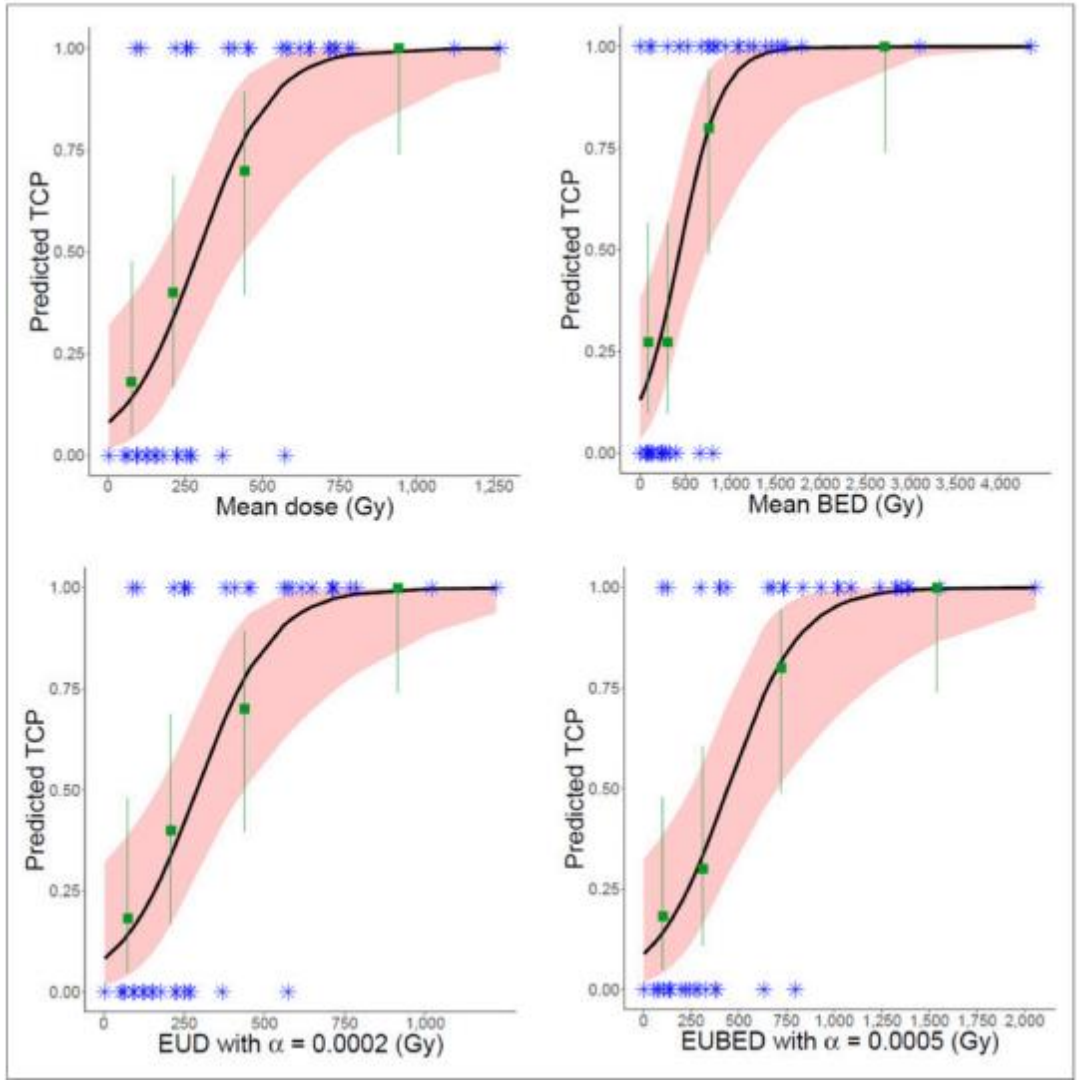
Glass spheres, HCC and differents liver mets

Dewaraja Y et al., 2019

TCP analysis by a logistic function

$$TCP_{jk} = \frac{e^{\beta_0 + b_{0k} + \beta_1 * AD_{jk}}}{1 + e^{\beta_0 + b_{0k} + \beta_1 * AD_{jk}}}$$

28 pts,
89 lesions



TCP (95%confidence intervals) vs. dose, BED, EUD and EUBED.
α : (0.1 to 0.0001) $\rightarrow$ for a good fit:
0.0001-0.002 Gy^{-1}

HCC and
Liveer mets

?

EUBED: better discrimination between responding and non responding lesions; absorbed dose is also a good parameter

Logit model TCP predictions compared with observed response proportions (green squares) by dose quartiles. Blue asterisk indicates observed binary response for each lesion. Pink shaded region shows 95% confidence interval for model, and green lines indicate score-based 95% confidence intervals for observations

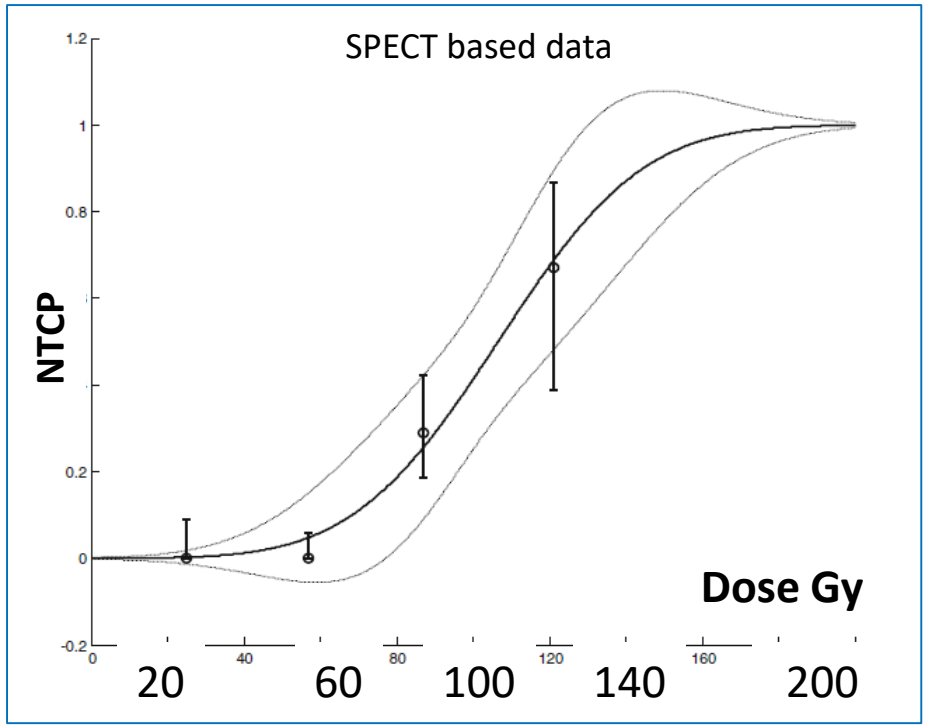
resin spheres – liver mets

Willowson K, et al. EJNMMI Res. 2017;7(1):46 Clinical and imaging-based prognostic factors in radioembolisation of liver metastases from colorectal cancer: a retrospective exploratory analysis.	**50 Gy** **PR/CR**	22 pts 63 lesions
van den Hoven AF, et al. JNM. 2016;57(7):1014-9 Insights into the Dose-Response Relationship of Radioembolization with Resin 90Y-Microspheres: A Prospective Cohort Study in Patients with Colorectal Cancer Liver Metastases.	**40-60 Gy** **ΔTLG >50%**	30 pts 113 lesions
Flamen P, et al. PMB 2008;53:6591-603 Multimodality imaging can predict the metabolic response of unresectable colorectel livermetastases to radioembolization therapy with yttrium-90 Labeled resin micropheres.	**65 Gy** **ΔTLG >50%**	8 pts 39 lesions
Rhee TK, et al. Ann Surg 2008;24 7:1029-35. 90Y Radioembolization for metastatic neuroendocrine liver tumors: preliminary results from a multi-institutional experience.	**110 Gy** **SD/PR**	22 pts
Lau WY, et al. IJROBP 2012;82(1):401-7 Patient selection and activity planning guide for selective internal radiotherapy with yttrium-90 resin microspheres.	**120 Gy** **PR/CR**	
Campbell JM, et al. IJROBP 2009; 74 :313-20. Early dose response to yttrium-90 microsphere treatment of metastatic liver cancer by a patient-speci®c method using single photon emission computed tomography and positron emission tomography.	**250 Gy** **CR**	14 pts 2 lesions

glass spheres - HCC

Chiesa C, Mira M, Maccauro M, et al.
Radioembolization of hepatocarcinoma with (90)Y glass microspheres: development of an individualized treatment planning strategy based on dosimetry and radiobiology. Eur J Nucl Med Mol Imaging. 2015;42(11):1718-1738.

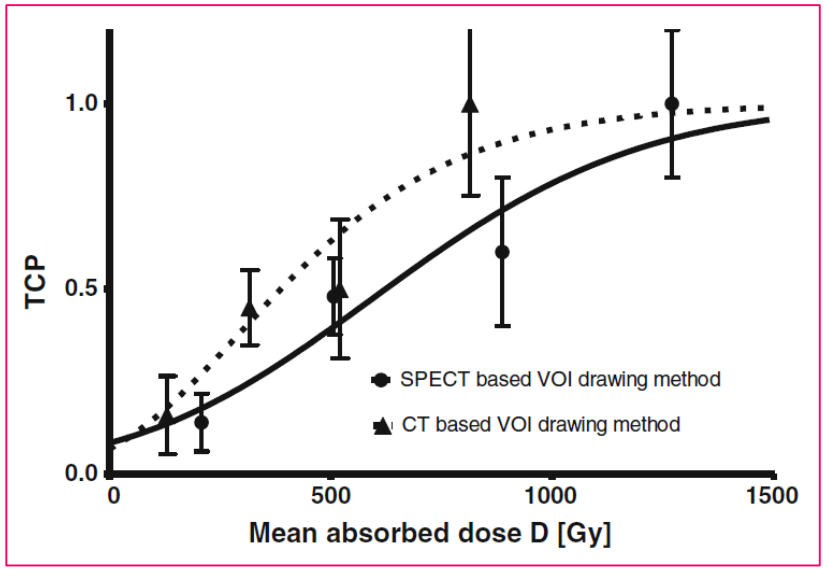
Liver toxicity

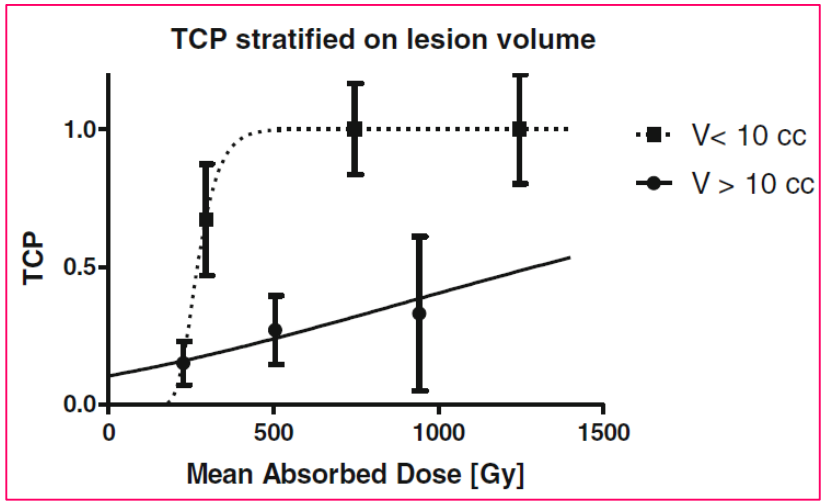


Limite ~ **70 Gy** per pazienti Child A5 → **15% rischio** scompenso (sfere di vetro somministrate dopo 3.75 gg)

EASL response CR, PR correlated with D (r = 0.6; 95%, P <0.001).
Non responding T: **D < 275 Gy**, responding T: **D >490 Gy** (P <0.001).
A threshold of 500 Gy → 20% non-responder rate (AUC=0.78)

Tumour Response - EASL





resin spheres - HCC

J Nucl Med. 2010 Sep;51(9):1377-85.

Efficacy and toxicity related to treatment of hepatocellular carcinoma with 90Y-SIR spheres: radiobiologic considerations.

Strigari L, Sciuto R, Rea S, Carpanese L, Pizzi G, Soriani A, Iaccarino G, Benassi M, Ettorre GM, Maini CL.

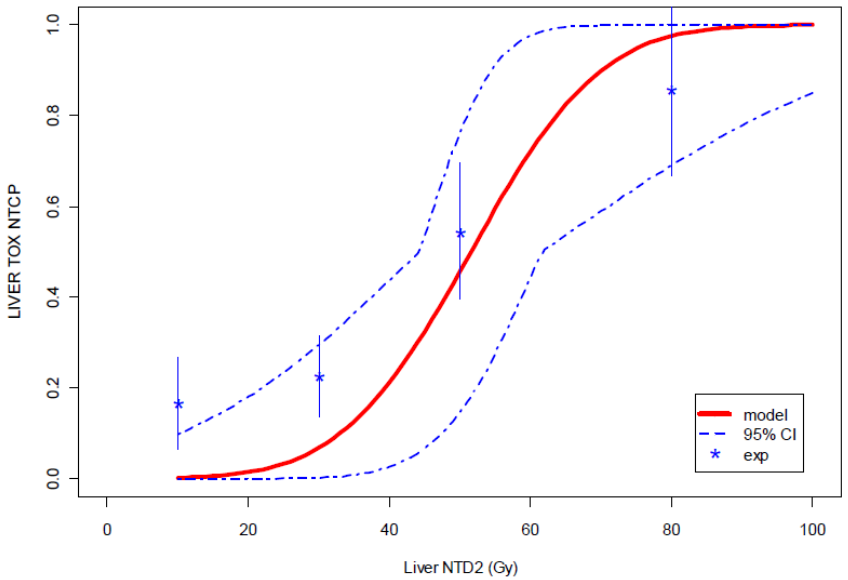
73 HCC patients

TD_{50} = 52 Gy

BED - liver: α/β = 2.5 Gy, T_{rep}= 2.5 h; Tumour: α/β = 10 Gy, T_{rep}= 1.5 h

Liver toxicity: NTCP - Lyman-Burman-Kutcher

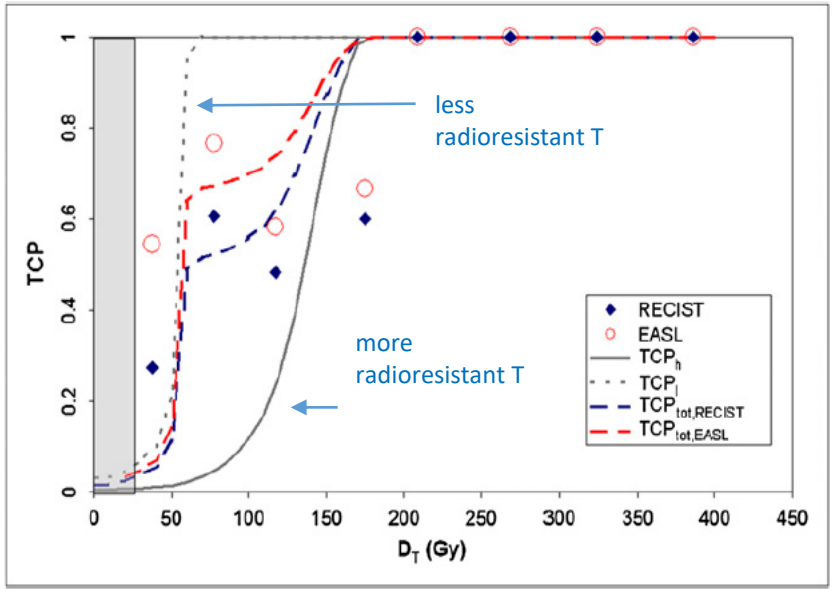
(n=1), endpoint: toxicity > G1



TD_{50} = 52 Gy (95% CI, 44±61 Gy),

m = 0.28 Gy^{-1}(95% CI, 0.18±0.60), slope vs. dose

Tumour response: TCP - RECIST and EASL criteria



TCP fitted with the Hp of 2 different cellular T radiosensitivity, obtaining 2 α-values (0.001 and 0.05 G y), lower than in EBRT (α =0.010.1/Gy) - Tai et al.

@ **D>200 Gy: CR or PR.**

D<200 Gy, higher response with EASL (changing T structure) vs. RECIST criteria (T shrinking).

@ D = 110 Gy, CR or PR: 74% (EASL), 55% (RECIST).

Traitement combiné de 2 radiopharmaceutiques pour NHL

based on Dose, EUD, EUBED

***Hobbs** RF, et al. Radiobiologic optimization of combination radiopharmaceutical therapy applied to myeloablative treatment of non-Hodgkin lymphoma. J Nucl Med. 2013;54(9):1535-42.*

methodology to hypothetical myeloablative treatment of NHL patients using **^{131}I-tositumomab, or Bexxar (B) and ^{90}Y-ibritumomab tiuxetan, or Zevalin**

$$\begin{cases} MTD_{lu} = A_Z d_{Z,lu} + A_B d_{B,lu} \\ MTD_{li} = A_Z d_{Z,li} + A_B d_{B,li} \end{cases}$$

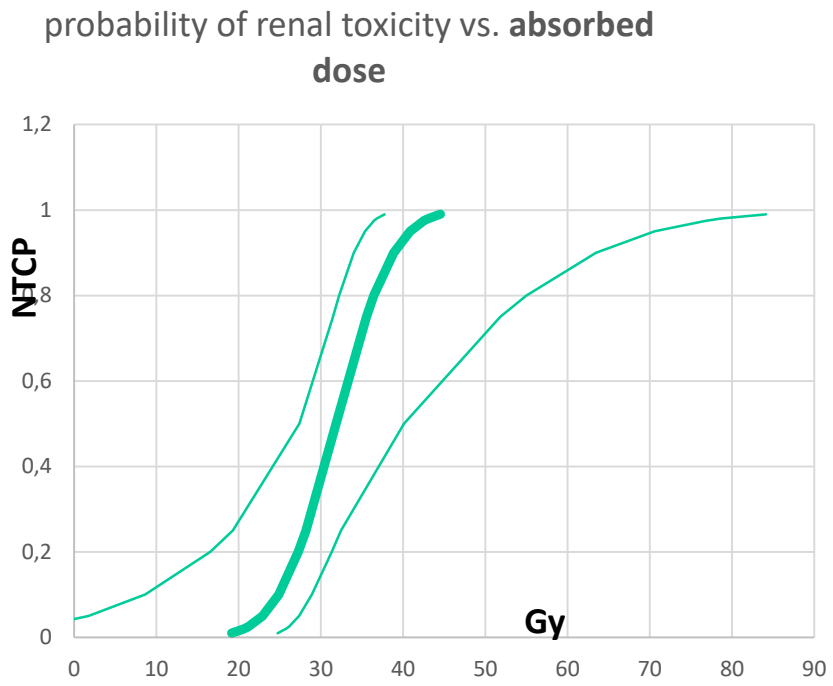
Radiobiologic Parameters Used

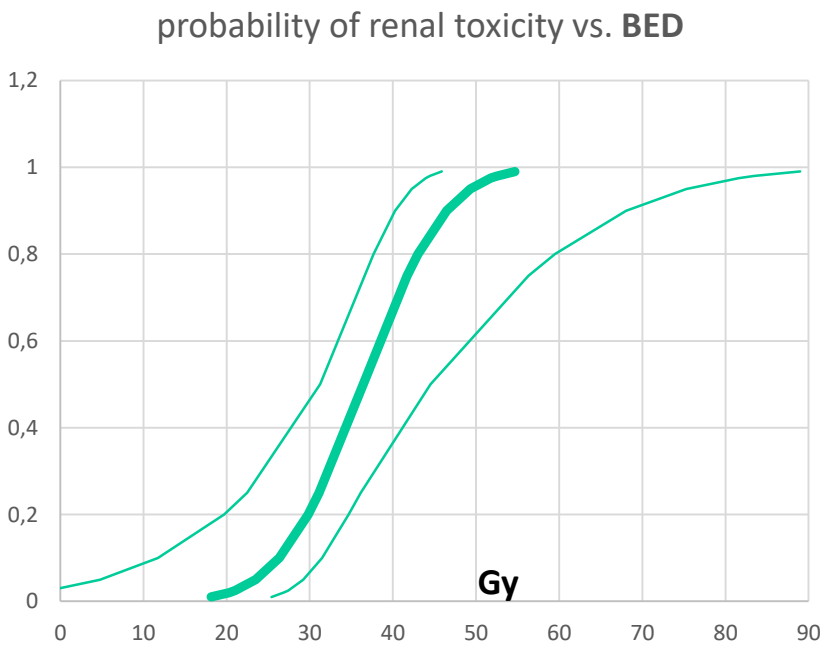
Parameter	NHL	Lungs	Liver	Kidneys
α/β (Gy)	8.6 (*28*)	3.3 (*29*)	2.5 (*30*)	2.6 (*18*)
λ_B (h^{-1})	N/A	0.0106 (*31*)	0.0124 (*31*)	0.0115 (*31*)
λ_Z (h^{-1})	N/A	0.0182 (*32*)	0.00728 (*32*)	0.00957 (*32*)
μ (h^{-1})	1.3 (*33*)	0.46 (*34*)	0.28 (*35*)	0.25 (*18*)

Tandem PRRT avec ^{177}Lu-DOTATOC and ^{90}Y-DOTATOC

Le BED a été utilisé pour combiner les effects des deux RIV avec différents radionucéides et dose/cycle

Only grades I-II of kidney toxicity in the majority of cases





Absorbed dose **TD_5 = 23 Gy**
TD_{50} = 32 Gy

BED **$TBED_5$ = 23 Gy**
$TBED_{50}$ = 36 Gy

Preliminary data by Grassi et al. (EANM 2017)