2nd Symposium on Molecular Radiotherapy Dosimetry:
The future of theragnostics
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Radiobiology including absorbed dose-effect relationship

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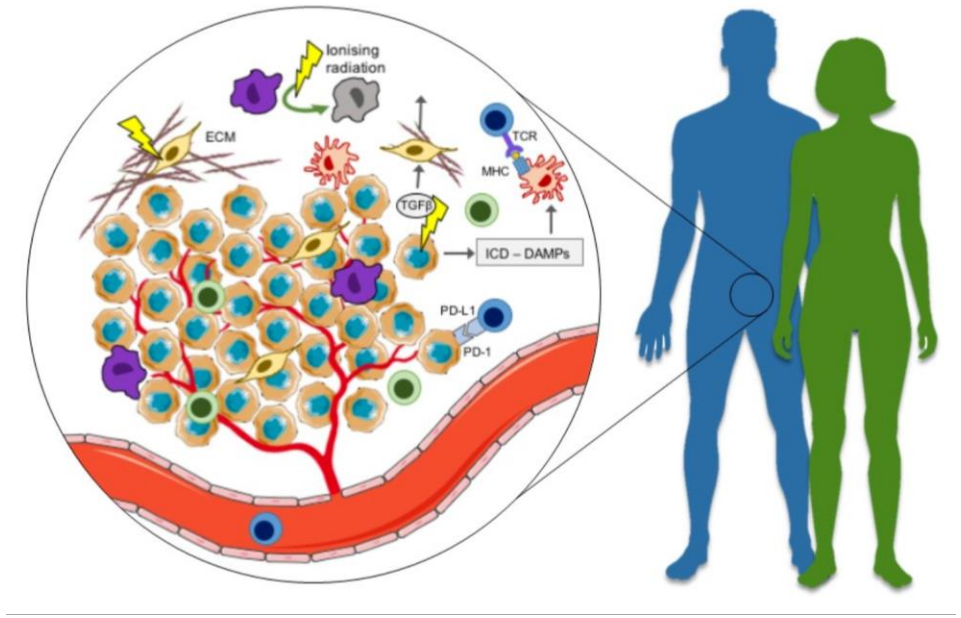
EFOMP

SIG
RADIONUCLIDE INTERNAL DOSIMETRY

Disclosure of Interest

There are no conflicts of interest to disclose.

Molecular Radiotherapy is the physical response to a biological problem.

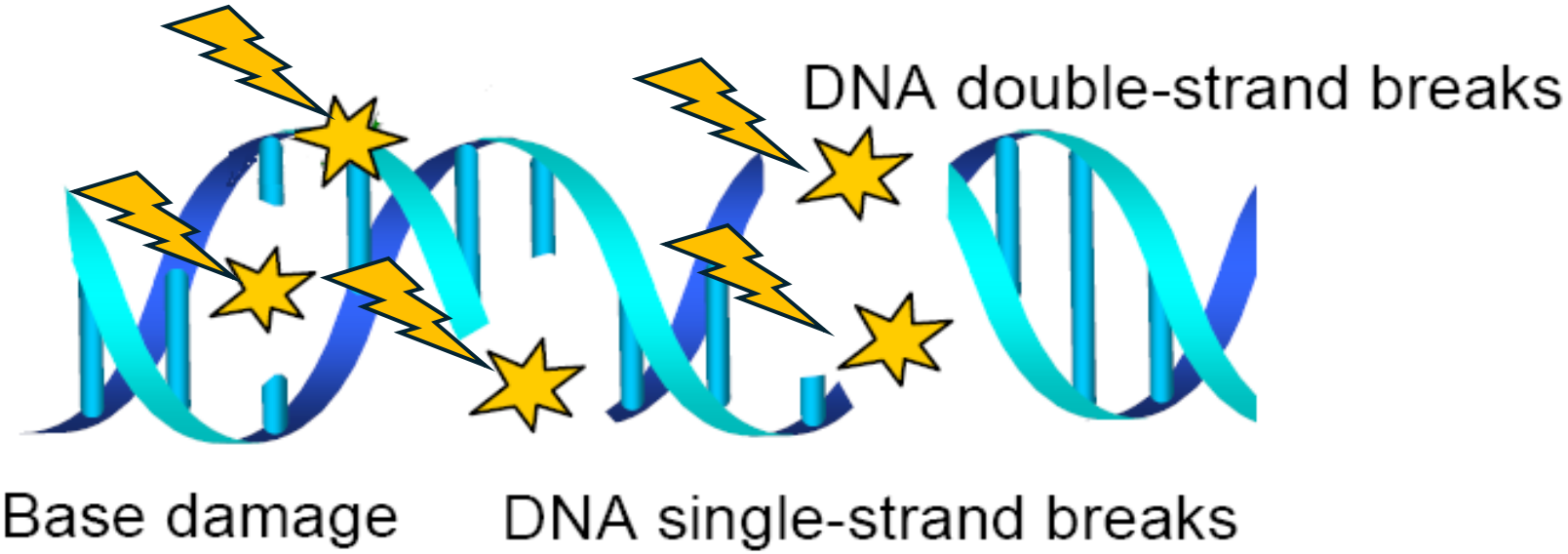


- The main goal of radiotherapy is to kill tumour cells, sparing normal tissues.
- Toxicity is a limiting factor
- Efficacy depends on
  - radio-sensitivity of various tumours
  - Identified pathways to induce tumour sterilisation (e.g., apoptosis, mitotic cell death, …)

Radiation damages to biomolecules

Direct

Indirect

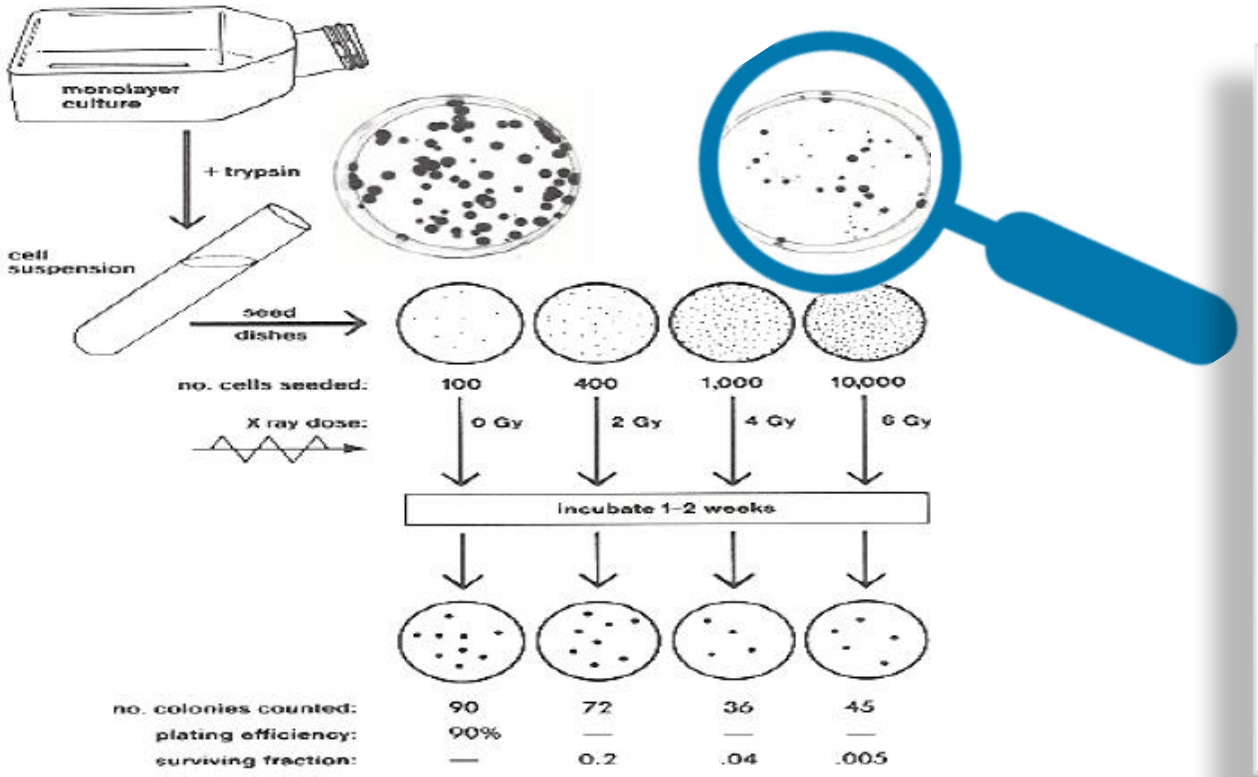


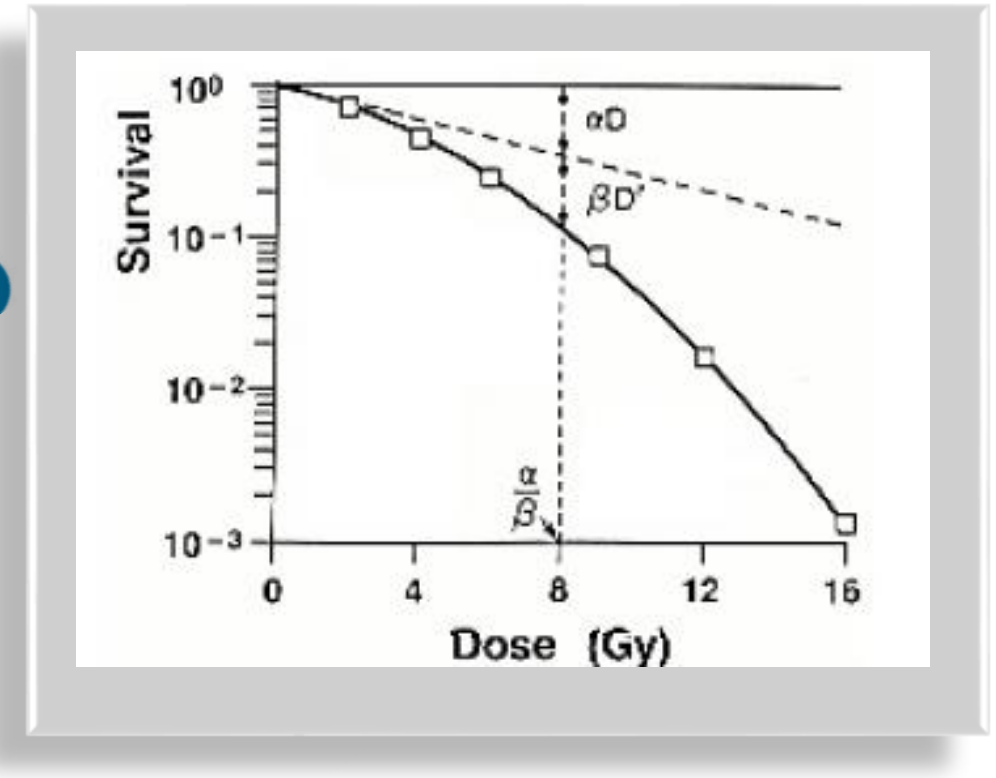
Types of DNA damage:	Approx. No. per gray:
1. Base damage	1000 – 2000
2. Single-strand breaks (ssb)	1000
3. Double-strand breaks (dsb)	40 ←

Radiation hit a cell nucleaus

- Mutation repaired → No effect
- Cell dies → Deterministic Effect
- Cell survive mutated → Stochastic Effect

Surviving fraction: cells are able to make “colonies”





$$S = N(D)/N_0$$

$S < (10^{-3} - 10^{-4})$

$$\ln(S) = -\alpha D - \beta D^2$$

$$-\ln(S) = effect$$

Relationship between α/β ratio and tissue response to fractionation

$$\ln(S) = -\alpha D - \beta D^2$$

tissue response to fractionation.

- **Large α/β (~10 Gy)** → *"Early-responding" tissues*: relatively **insensitive to dose per fraction**, such as mucosa, skin, and most tumors.
- **Small α/β (< ~4 Gy)** → *"Late-responding" tissues*: **sensitive to dose per fraction**, including liver, lung, and kidney.

Typical values of α values is hard to measure vs α/β

- α values is hard to measure vs α/β. e.g. for low LET radiation
  - α value: 0.1 Gy^{-1} – 1.5 Gy^{-1}
  - α/β value: 1.0 Gy – 20 Gy

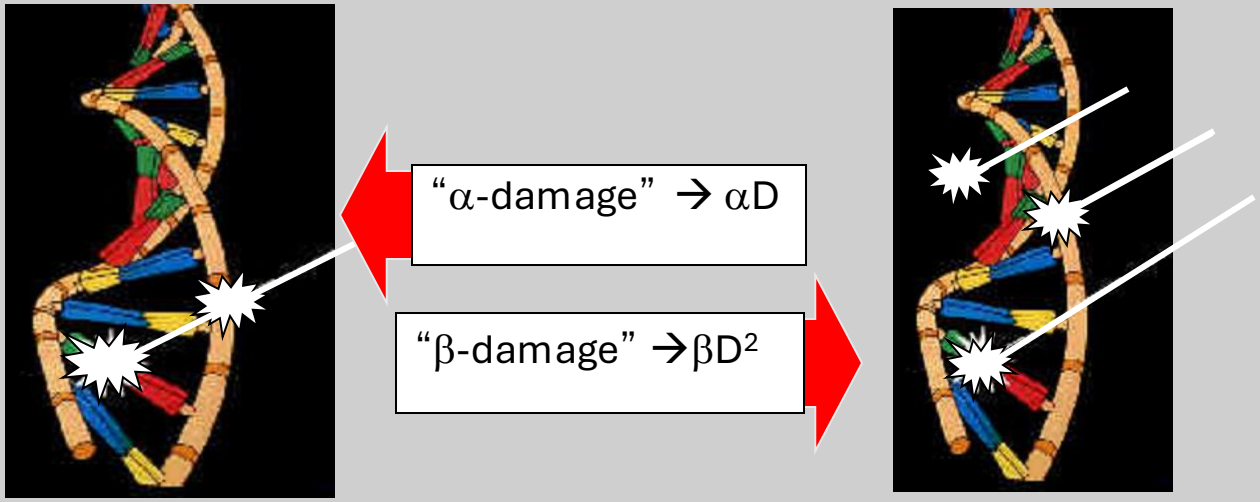
Repopulating tissues

- **Liver**
- **Slow-growing neoplasms**, including **prostate tumors** and others (e.g., **thyroid**)

Biological effective dose & EQDx concepts

BED

Linear Quadratic model



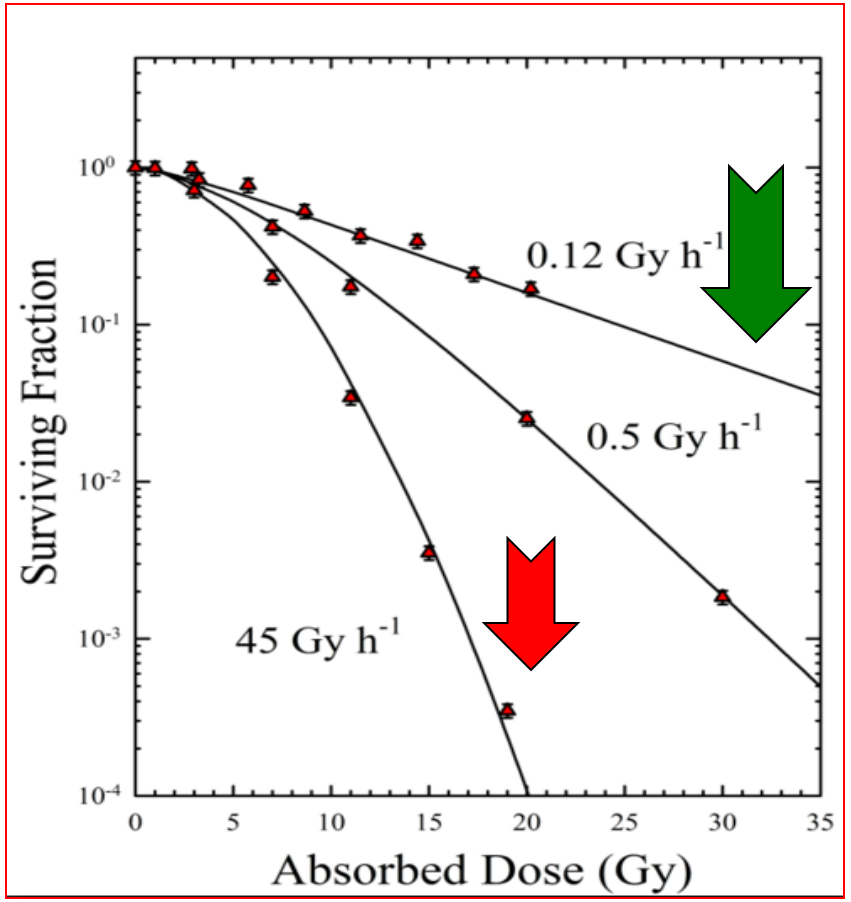
$$BED = D + \beta/\alpha \cdot \frac{T_{1/2rep}}{T_{1/2rep} + T_{1/2eff}} \cdot D^2$$

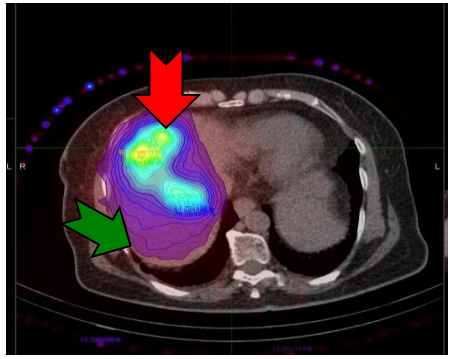
$T_{1/2\ rep}$ = **1.5 h / 0.5 h** → repair half-life

normal tissues / tumors

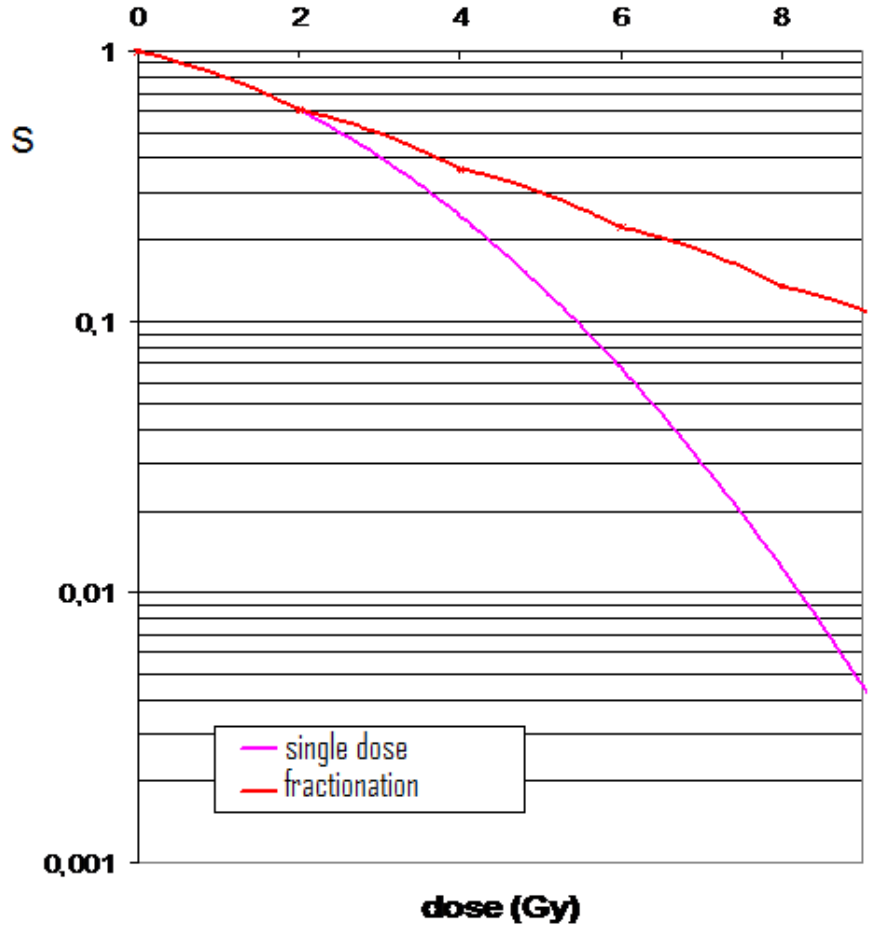
$T_{1/2\ eff}$ = **effective half time of radionuclide**

Local dose-rates





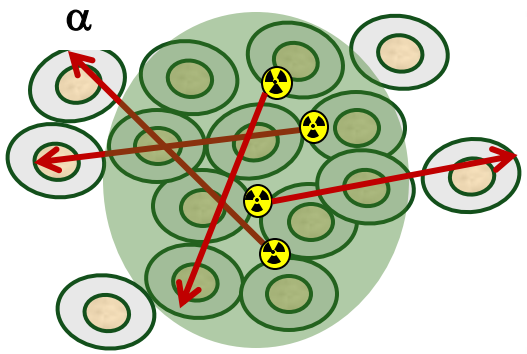
Cell repopulation

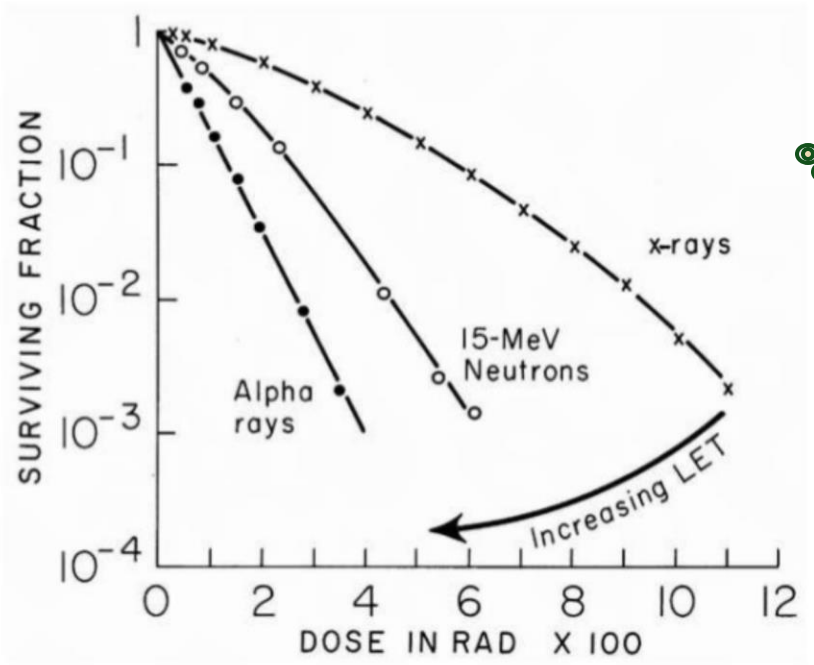


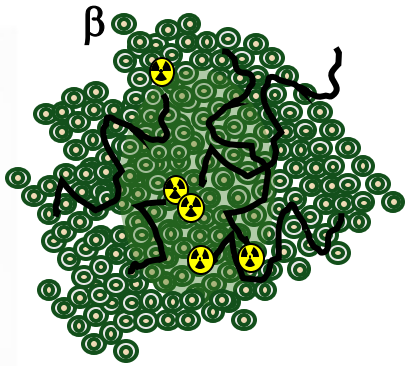
Relative biological effectiveness (RBE)

RBE is defined as the dose D by using **α-particles** required to generate the same survival (S) as the reference dose D_γ (delivered by the reference γ radiation).

Effect of LET on cell survival







$$RBE = \left.\frac{D_\gamma}{D}\right|_{SF}$$

$$sRBEx = \left.\frac{\kappa}{\alpha+\beta X}\right|_{SF}$$

ICRU REPORT No. 96

Adapted from Hall 2006, Kassis Sem Nucl Med 2008

Biological effective dose

Fractionation: the number of cycles

Time interval between cycles

Administered activity

Dose rate: The quantity of radiation absorbed per unit time $\dot{D}$

Tissue radiosensitivity (α/β) Repopulation (T_{av})

Absorbed Dose: The quantity of energy per mass unit absorbed during treatment D_T

Type of radiation/particle

LQ Model

local dose-rates produce different radiobiological effects

The expression for the BED becomes

$$\mathrm{BED} = D\left(1+\frac{G(\tau)}{\alpha/\beta}D\right)-K\cdot\tau, \qquad (4.15)$$

where K is a parameter to offset tumor repopulation and τ is the effective time of treatment. The latter term in Eq. (4.15) has been named the repopulation factor (RF) (Dale, 1989).

Repopulation reduces the treatment efficacy

ICRU REPORT No. 96

Fractionation: the number of cycles

Time interval between cycles

Administered activity

Dose rate: The quantity of radiation absorbed per unit time $\dot{D}$

Tissue radiosensitivity (α/β) Repopulation (T_{av})

Absorbed Dose: The quantity of energy per mass unit absorbed during treatment D_T

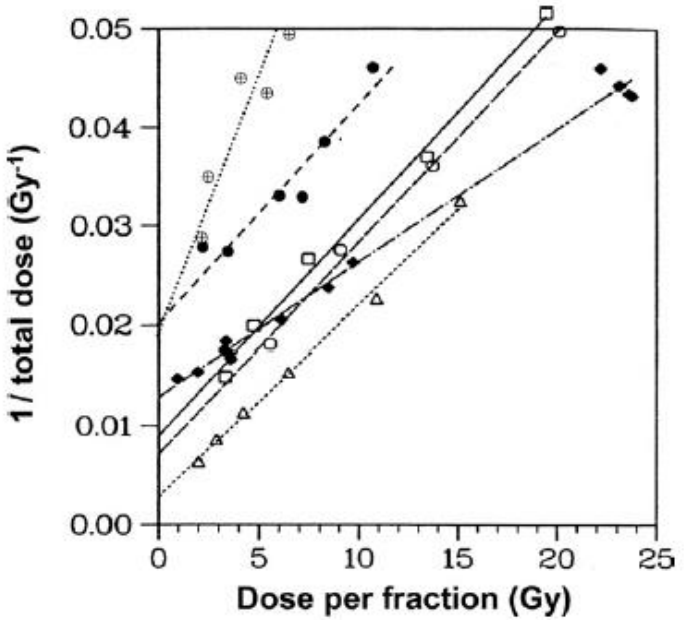
Type of radiation /particle

LQ Model

Iso-effects

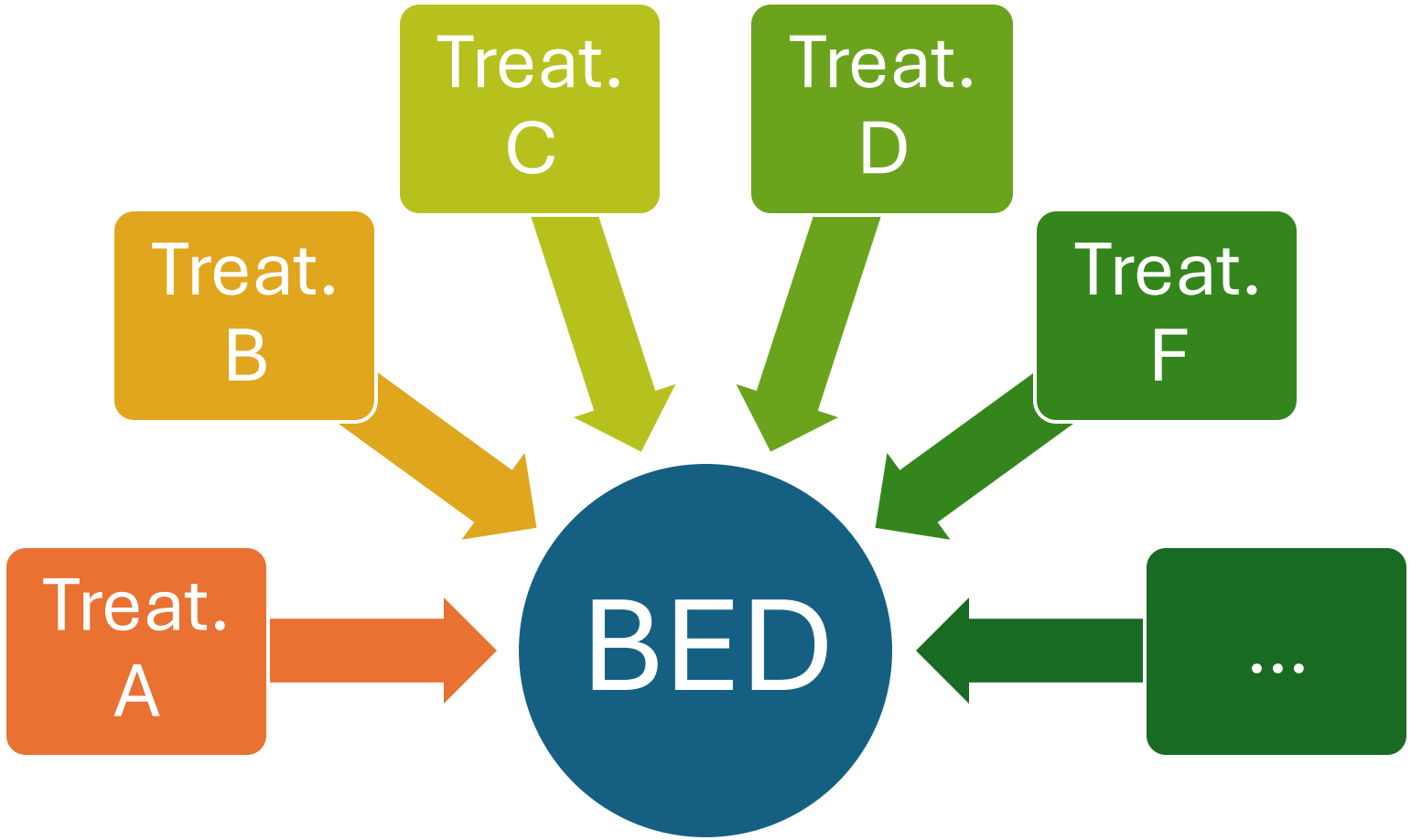
Withers (1982) found that the efficacy depends on both the total dose (D) and dose per fraction (d).

$$\frac{effect}{\alpha} = \mathrm{BED} = \alpha D\left(1+\frac{d}{\alpha/\beta}\right)$$



BED: the radiobiological fulcrum of practical radiotherapy

- Number of cycles
- Intercycle interval
- Dose per cycle
- Overall time
- Dose-rate
- RBE (for high LET)
- α/β ratio



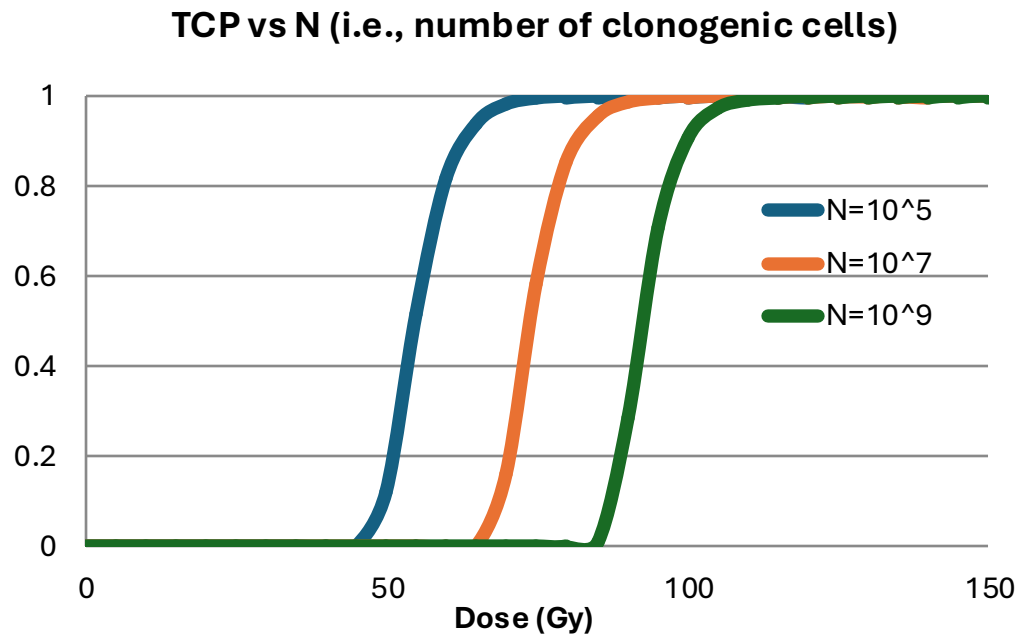
Poissonian-LQ-TCP-model

$$TCP = e^{-N_0^* \cdot S}$$

$$TCP = e^{-N_0^* \cdot \exp(-\alpha \cdot BED)}$$

Hypothesis:

Indipendence → clonogens



Large tumors need higher doses to be controlled

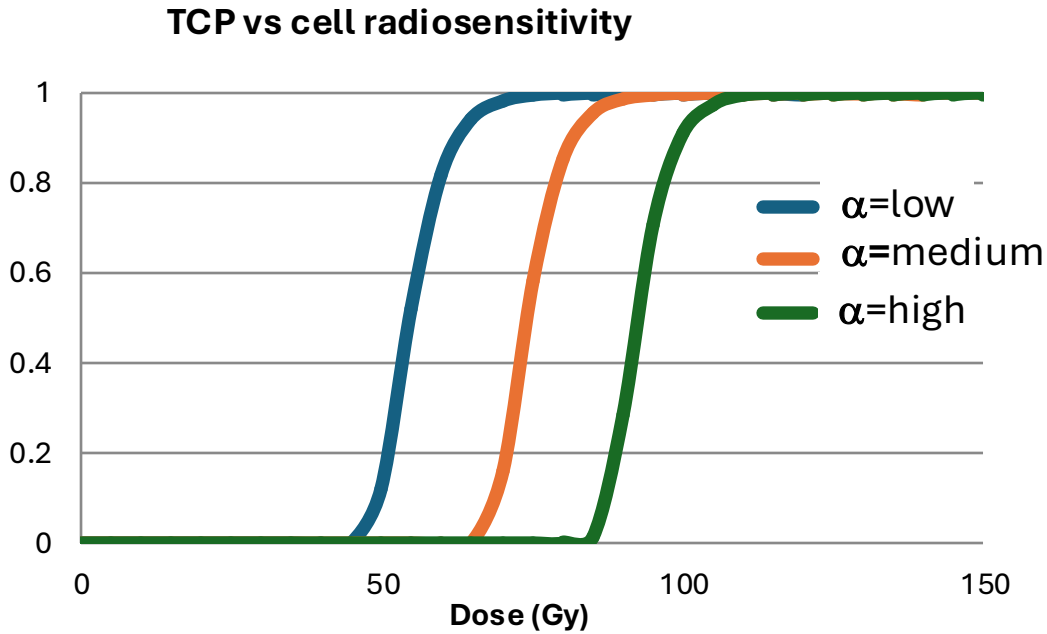
Poissonian-LQ-TCP-model

$$TCP = e^{-N_0^* \cdot \exp(-\alpha \cdot BED)}$$

Vascularization determines oxygenation and, therefore radiosensitivity

- Blood vessels play a very important role in determining radiation effects both for tumours and for normal tissues.

Hypoxic cells induced by radiation
Reoxygenated cells during treatment



Hypoxyc cells are more radioresistant tumoral cells

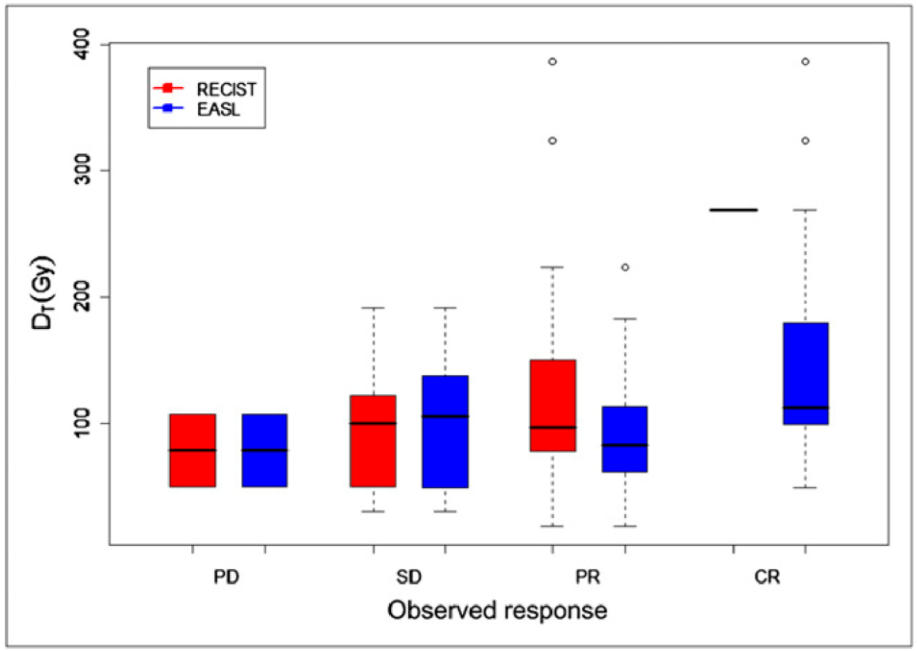
Efficacy and Toxicity Related to Treatment of Hepatocellular Carcinoma with ^{90}Y-SIR Spheres: Radiobiologic Considerations

Lidia Strigari[1], Rosa Sciuto[2], Sandra Rea[2], Livio Carpanese[3], Giuseppe Pizzi[3], Antonella Soriani[1], Giuseppe Iaccarino[1], Marcello Benassi[1], Giuseppe Maria Ettorre[4], and Carlo Ludovico Maini[2]

[1]Laboratory of Medical Physics and Expert Systems, Regina Elena National Cancer Institute, Rome, Italy; [2]Department of Nuclear Medicine, Regina Elena National Cancer Institute, Rome, Italy; [3]Department of Radiology, Regina Elena National Cancer Institute, Rome, Italy; and [4]Department of General Surgery and Liver Transplantation, Azienda Ospedaliera San Camillo-Forlanini, Rome, Italy

JNM 2010

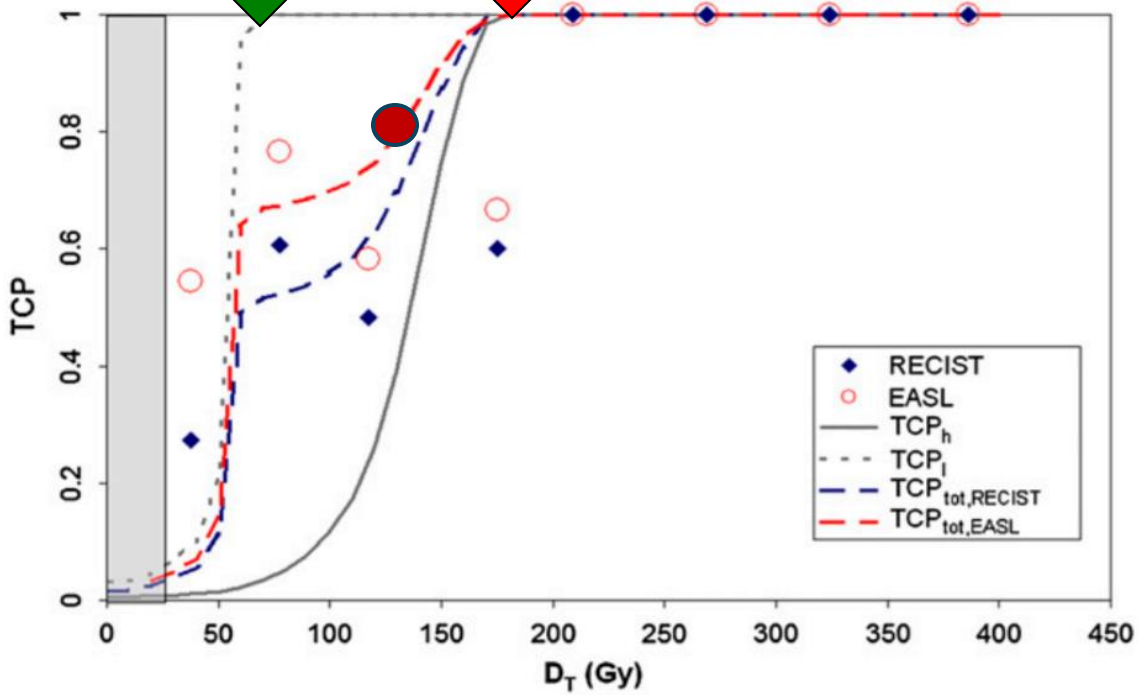
Dose-response model



$$TCP = e^{-N_0^* \cdot S}$$

Small lesion
Well oxygenated areas

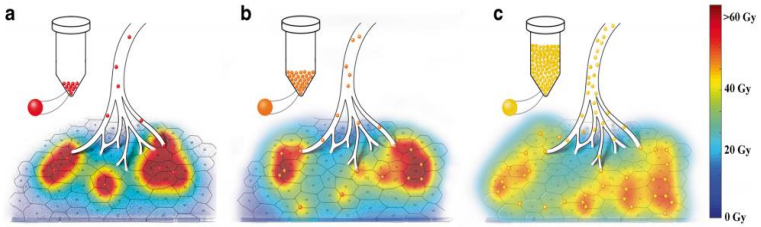
Large lesions
Hypoxic areas



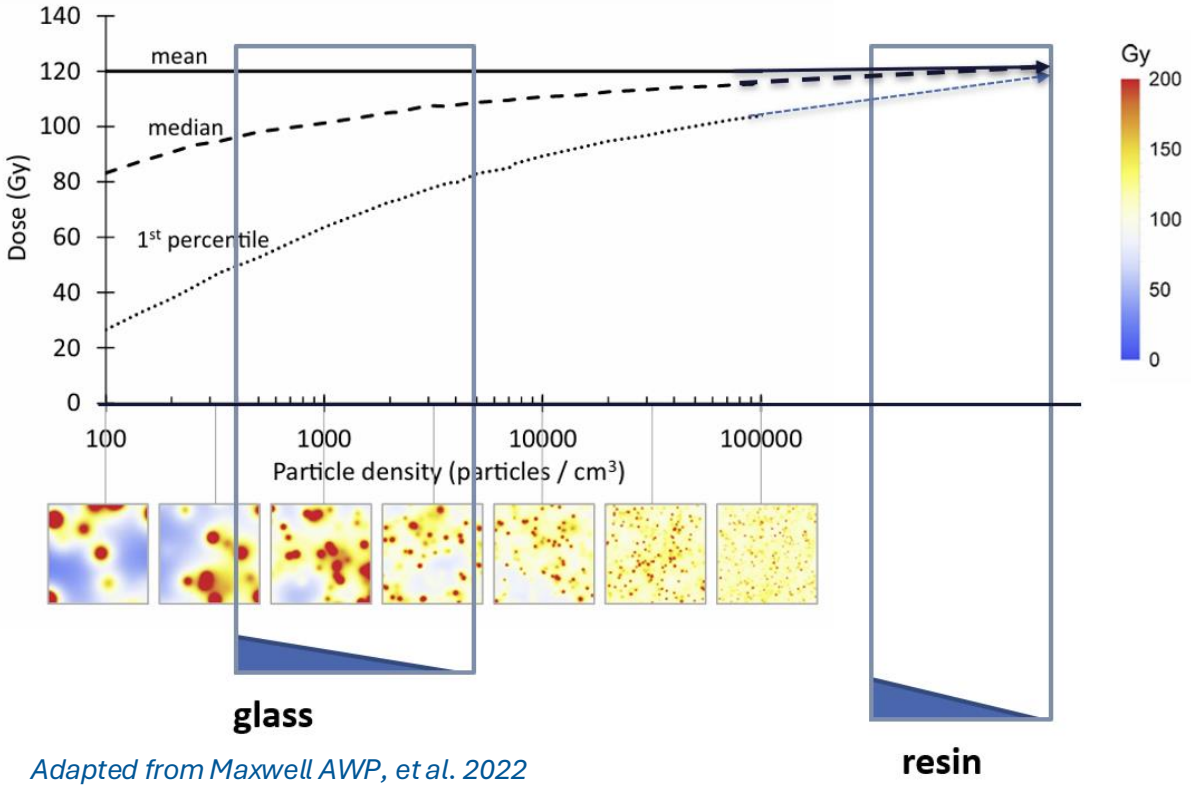
Impact of non-uniformity

- Activity (dose) distribution is not uniform
- Resin vs. glass spheres ≠ number of spheres

→ ≠ thresholds for response & toxicity



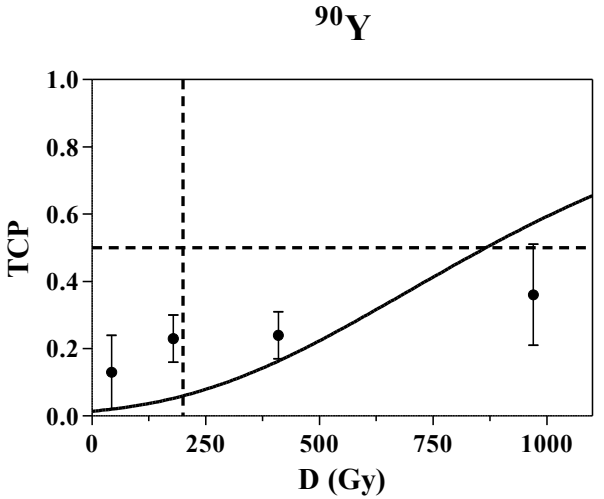
Pasciak AS, EJNMMI 2020; Högberg EJNMMI Res. 2014; Van der Gucht, JNM 2017; Walrand, JNM 2014

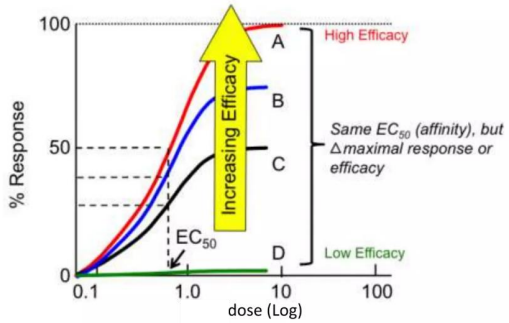


Adapted from Maxwell AWP, et al. 2022

Dose rate effect matters

- 166Ho- vs 90Y-based SIR
  - Early tumour response





•Drug A, B & C are equally potent but Drug A is more efficacious then drug B & C (Drug A>Drug B>Drug C)

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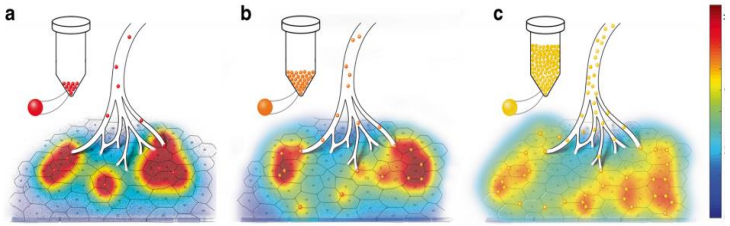

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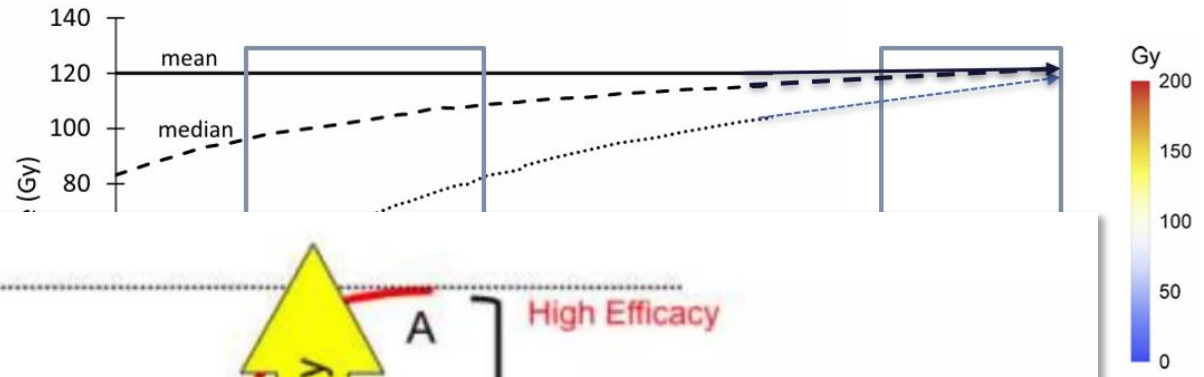

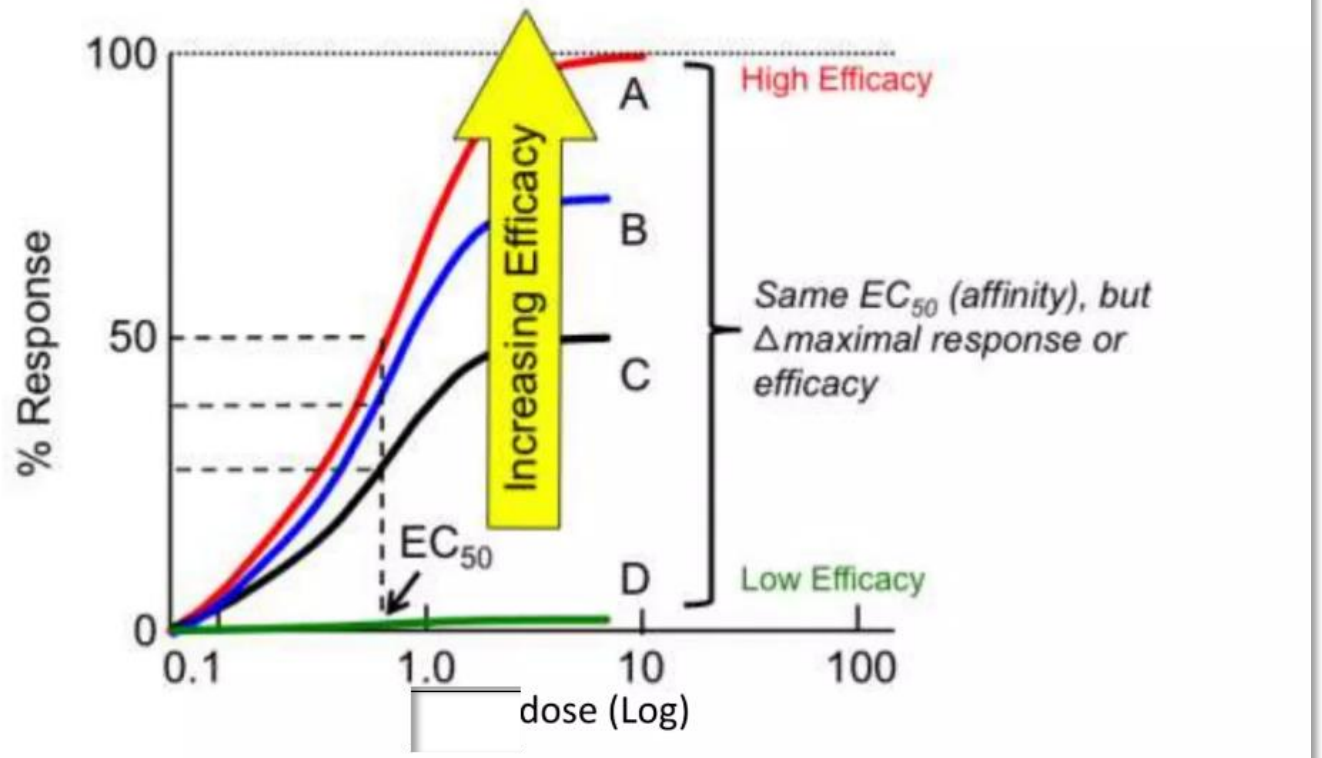

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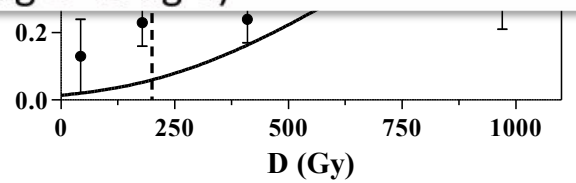


Several dose-effect correlations for NET tumours

doi:10.2967/jnumed.123.266991

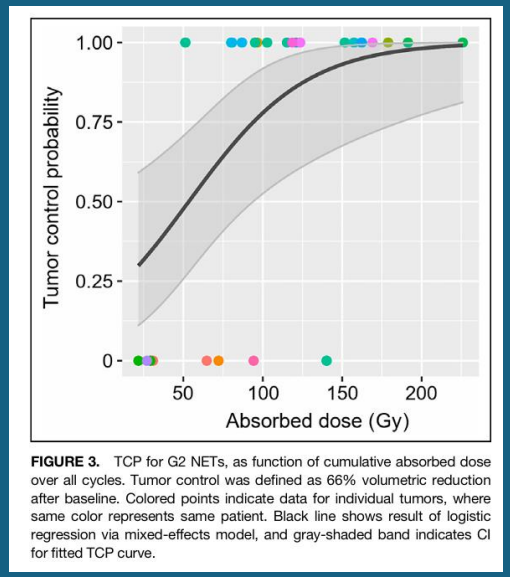
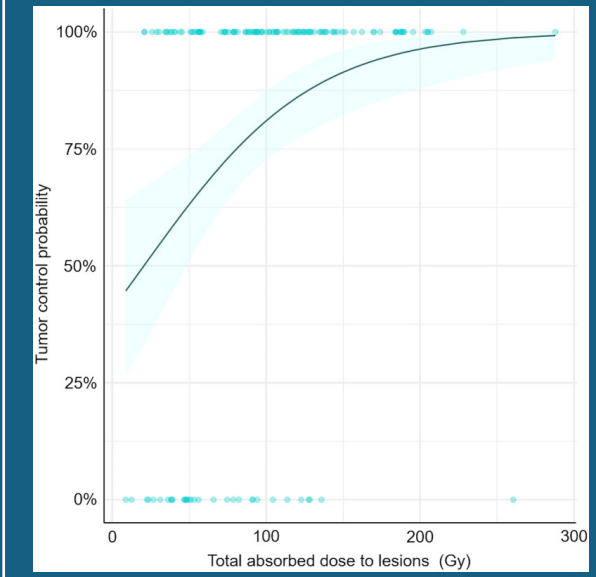


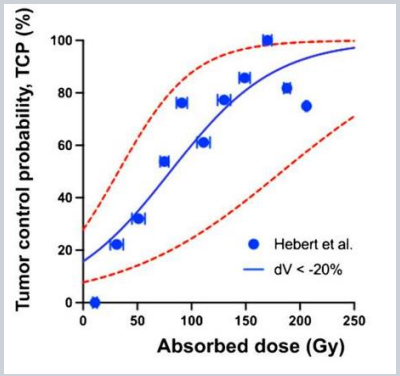
FIGURE 3. TCP for G2 NETs, as function of cumulative absorbed dose over all cycles. Tumor control was defined as 66% volumetric reduction after baseline. Colored points indicate data for individual tumors, where same color represents same patient. Black line shows result of logistic regression via mixed-effects model, and gray-shaded band indicates CI for fitted TCP curve.

TCP for G2 NETs,as function of cumulative absorbed dose overall cycles. Tumor control was defined as 66% volumetric reduction after baseline.
25% lesions

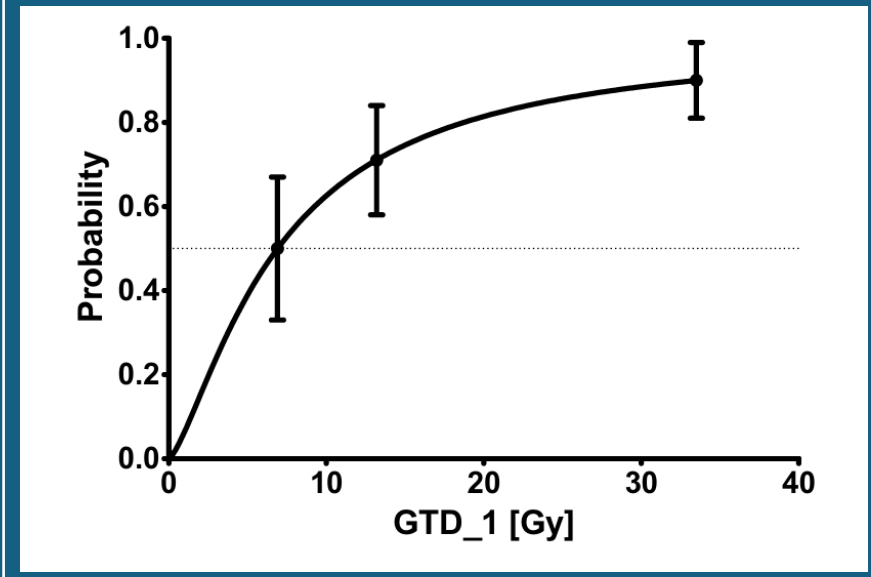
10.2967/jnumed.123.267023



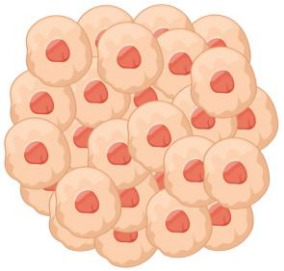
Variation of lesion volume ≤ 0% between baseline and M3-CT is considered as controlled tumor.



doi: 10.1007/s00259-025-07378-w.



Tumour Control Probability (TCP) as a function of Global Tumour Dose at cycle 1 (GTD_1). The tumour control was defined as having a PFS > = 24 m



Proliferative Organization of Normal Tissues

- Cell proliferation in normal tissues is highly organised, with cell production under tight homeostatic control.
- ***Number maintained by proliferative activity of precursor cells***, i.e. cells which serve to replace those cells lost due to normal "wear and tear".
- The degree of organisation of cells within proliferative and functional compartments has been used to distinguish between **two categories of tissues, hierarchical and flexible** (Michalowski 1981).

Hierarchical or H-type Tissues

(Flexible) F-type Tissues

Hierarchical or H-type tissues

Mostly rapidly renewing cell systems: include hematopoietic tissues, skin epidermis, GI tract mucosa and testicular epithelium.

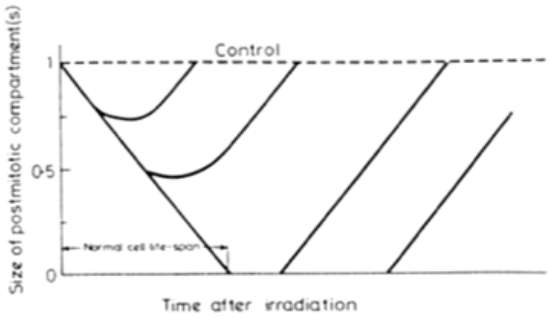
Stem cells * (self-renewing) → Precursors (amplification) → Mature cells (function)

Life span

Time to response

* Stem cell number is maintained by self-replication; when not proliferating, the stem cells reside in a quiescent G0 state

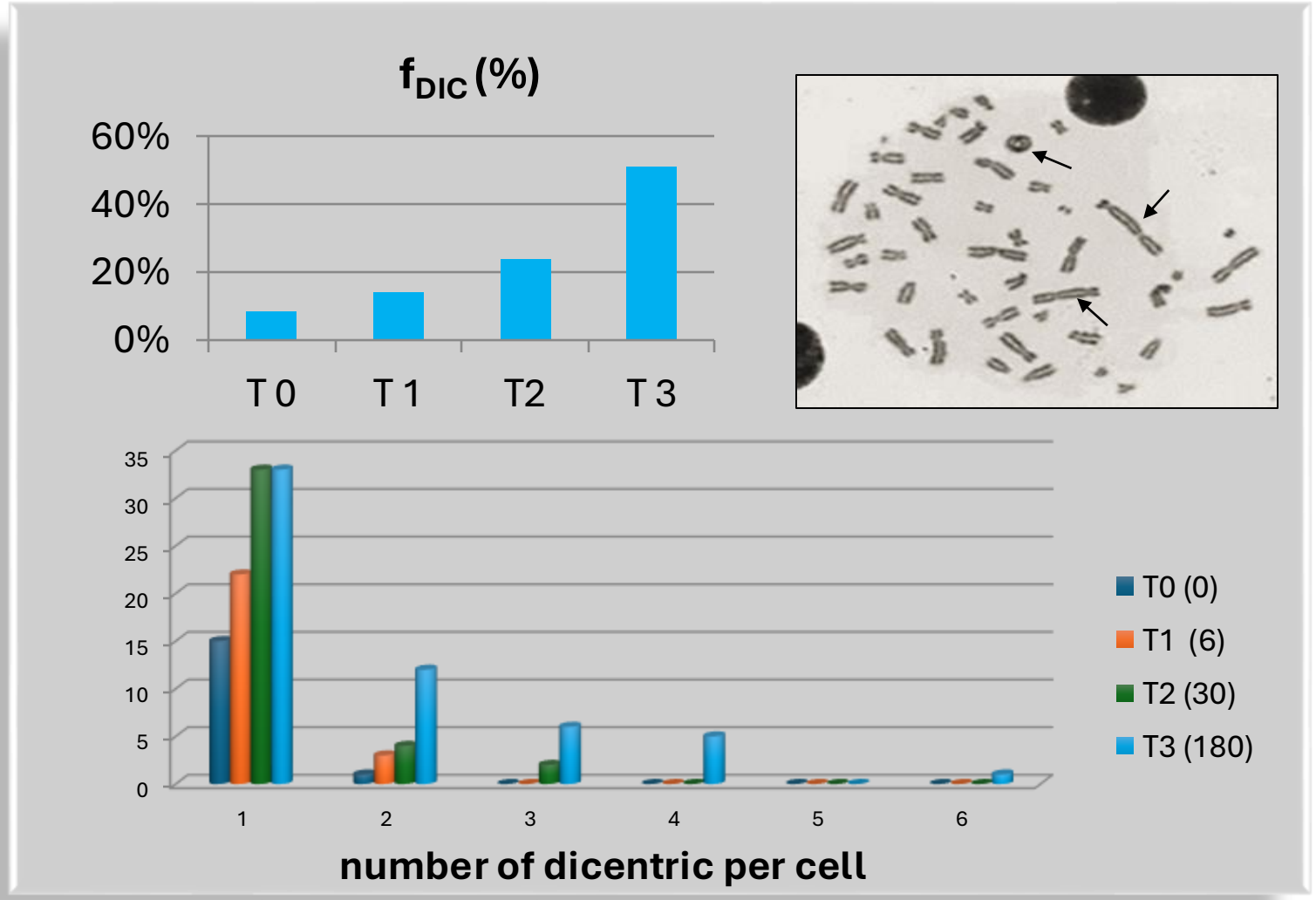
- Time to reach complete depopulation depends on the **length of mature cell longevity**, and it is **dose-independent**

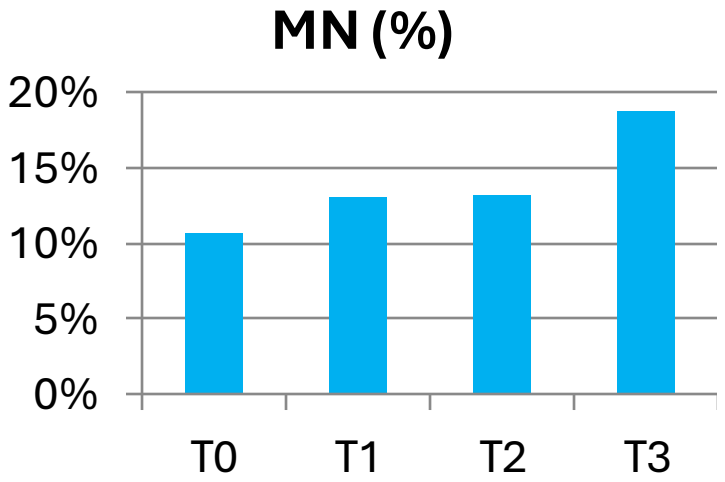


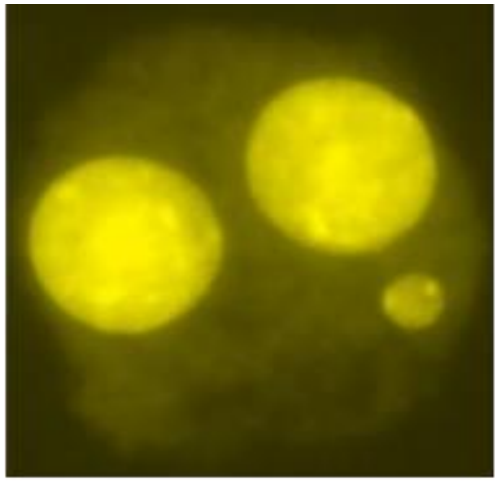
Steel GG, Basic clinical radiobiology

Hierarchical or H-type Tissues

Frequency of Dicentrics and Micronuclei in PBL of patients during $^{223}RaCl_2$ therapy



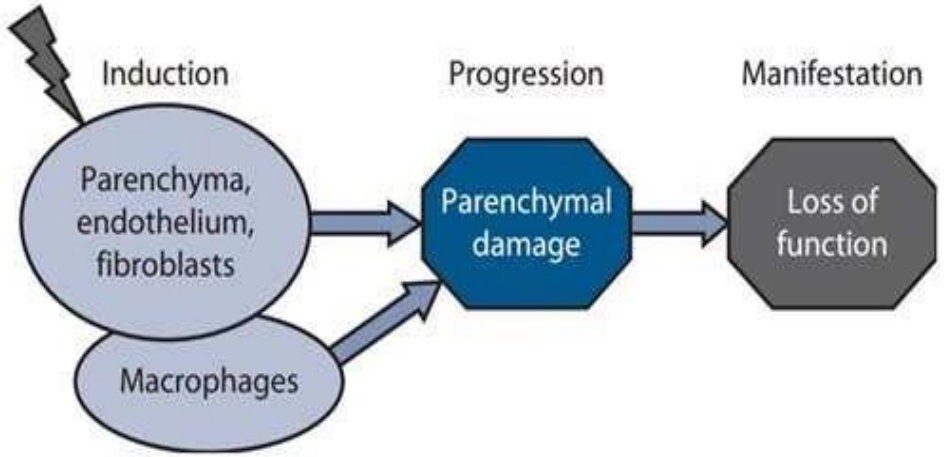




Radiation Response of (Flexible) F-type Tissues

Dose dependent

- Cell killing
- Probability of mitotic failure
- Steepness of initial slope of depopulation
- Rate of depopulation

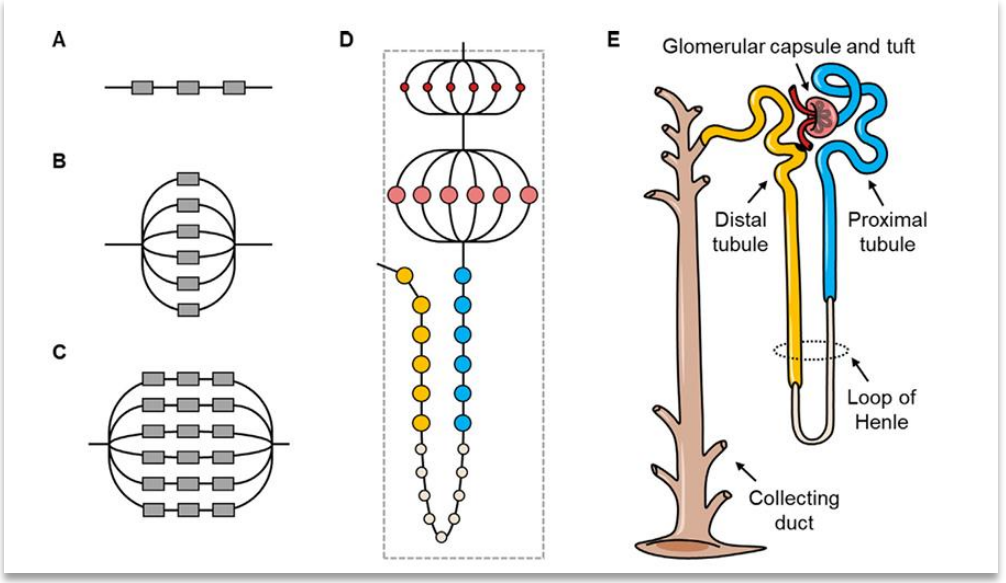


- These tissues (**e.g., liver, lung, kidney**) typically have **long turnover times**; thus, an apparent delay in the expression of damage may be seen, and its duration will be inversely related to dose.

- Therefore, **more severe damages are seen earlier than mild injury**, in contrast to the H-type tissue reactions (i.e., severe damages take less time to occur with increasing dose).

Different F-tissue architectures

- Serial (A)
- Parallel (B)
- Combined (C-E)



doi.org/10.1016/j.zemedi.2023.02.006

Effect of radiation on the organ is different

Sensitivity
Repair

➡ **Tolerance dose, α/β ratio**
➡ Time-related **recovery factors**: repair half-time, repopulation, long-term recovery

Repopulation
Migration

➡ **Volume effects**: cell migration, tissue compartment, injury probability

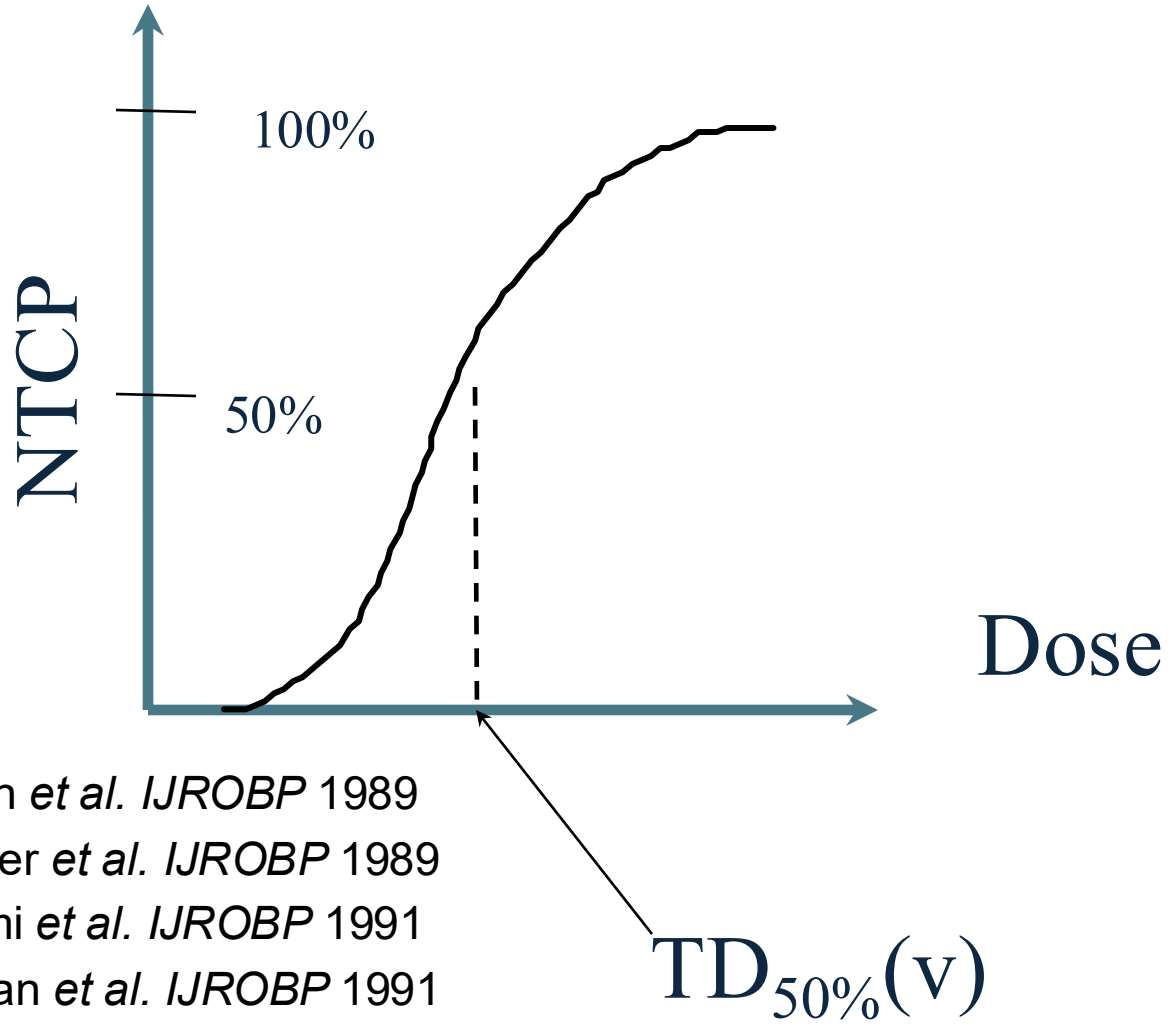
Percentage of patients with complication of a given grade

- **Lyman model**
- **4-parameter sigmoidal function for all complications**

$$s = \frac{D - TD_{50}(v_{eff})}{m\, TD_{50}(v_{eff})}$$

$$NTCP(s) = \frac{1}{\sqrt{2\pi}} \int_0^s \exp(-t^2/2)dt$$

- **Parameters:**
  - **$TD_{50}(1)$**
  - **m (and $TD_5(1)$)**
  - **effective volume v_{eff}**



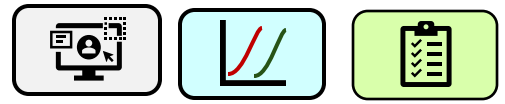
Lyman *et al. IJROBP* 1989
Kutcher *et al. IJROBP* 1989
Emami *et al. IJROBP* 1991
Burman *et al. IJROBP* 1991

Efficacy and Toxicity Related to Treatment of Hepatocellular Carcinoma with ^{90}Y-SIR Spheres: Radiobiologic Considerations

Lidia Strigari[1], Rosa Sciuto[2], Sandra Rea[2], Livio Carpanese[3], Giuseppe Pizzi[3], Antonella Soriani[1], Giuseppe Iaccarino[1], Marcello Benassi[1], Giuseppe Maria Ettorre[4], and Carlo Ludovico Maini[2]

[1]Laboratory of Medical Physics and Expert Systems, Regina Elena National Cancer Institute, Rome, Italy; [2]Department of Nuclear Medicine, Regina Elena National Cancer Institute, Rome, Italy; [3]Department of Radiology, Regina Elena National Cancer Institute, Rome, Italy; and [4]Department of General Surgery and Liver Transplantation, Azienda Ospedaliera San Camillo-Forlanini, Rome, Italy

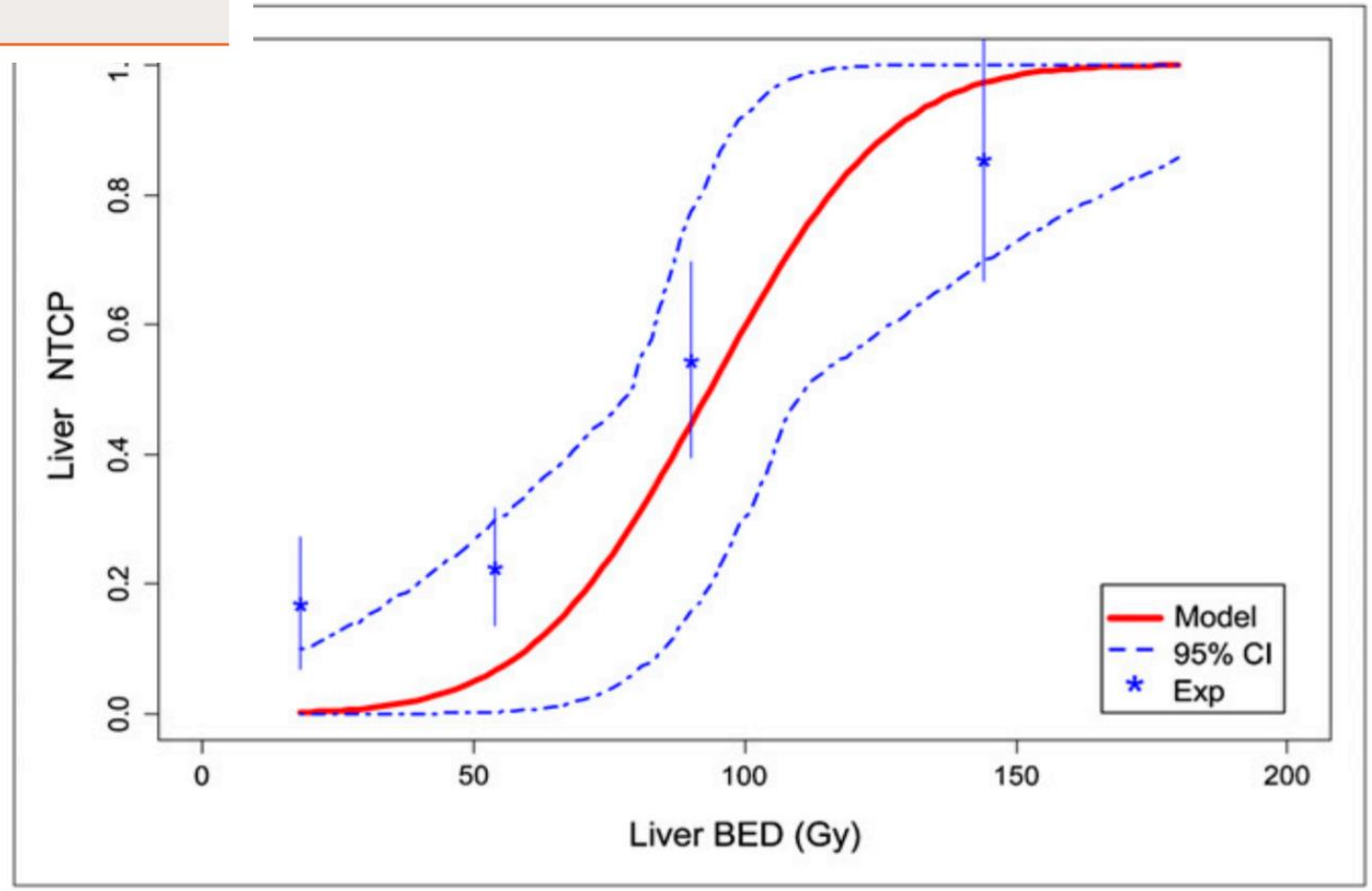
TCP/NTCP models



Follow-up Constraints

- JNM 2010

Post treatment dosimetry
allows developing predictive dose-response model



TCP/NTCP models

Follow-up

Constraints

A Hepatic Dose-Toxicity Model Opening the Way Toward Individualized Radioembolization Planning

Stephan Walrand, Michel Hesse, Francois Jamar, and Renaud Lhommel

Nuclear Medicine, Molecular Imaging, Radiotherapy, and Oncology Unit (MIRO), IECR, Université Catholique de Louvain, Brussels, Belgium

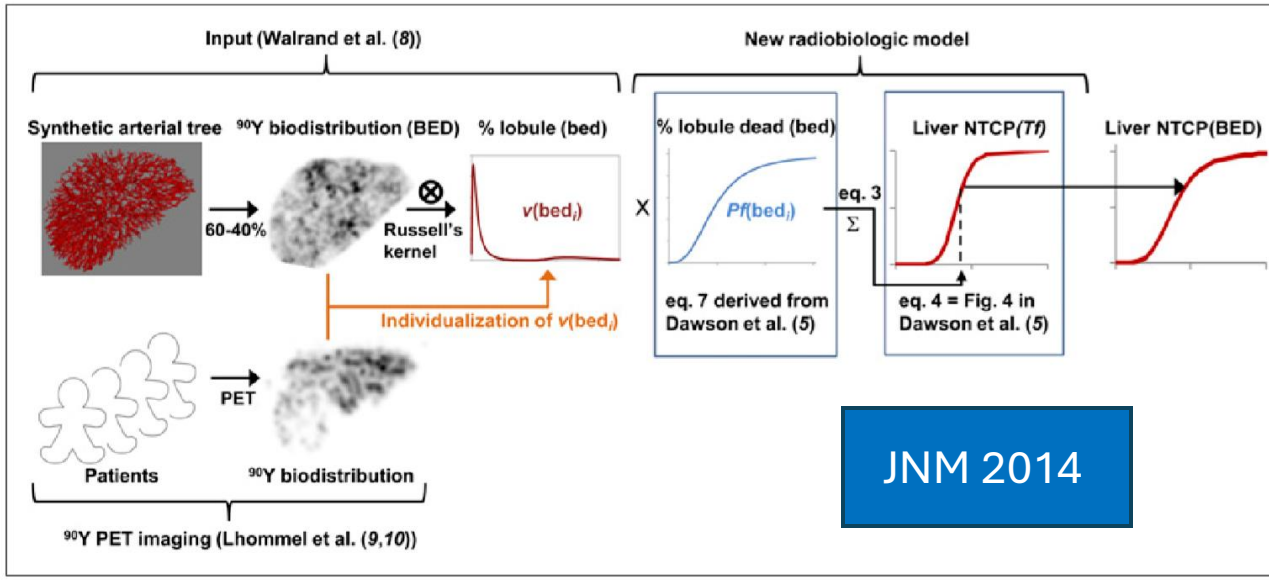
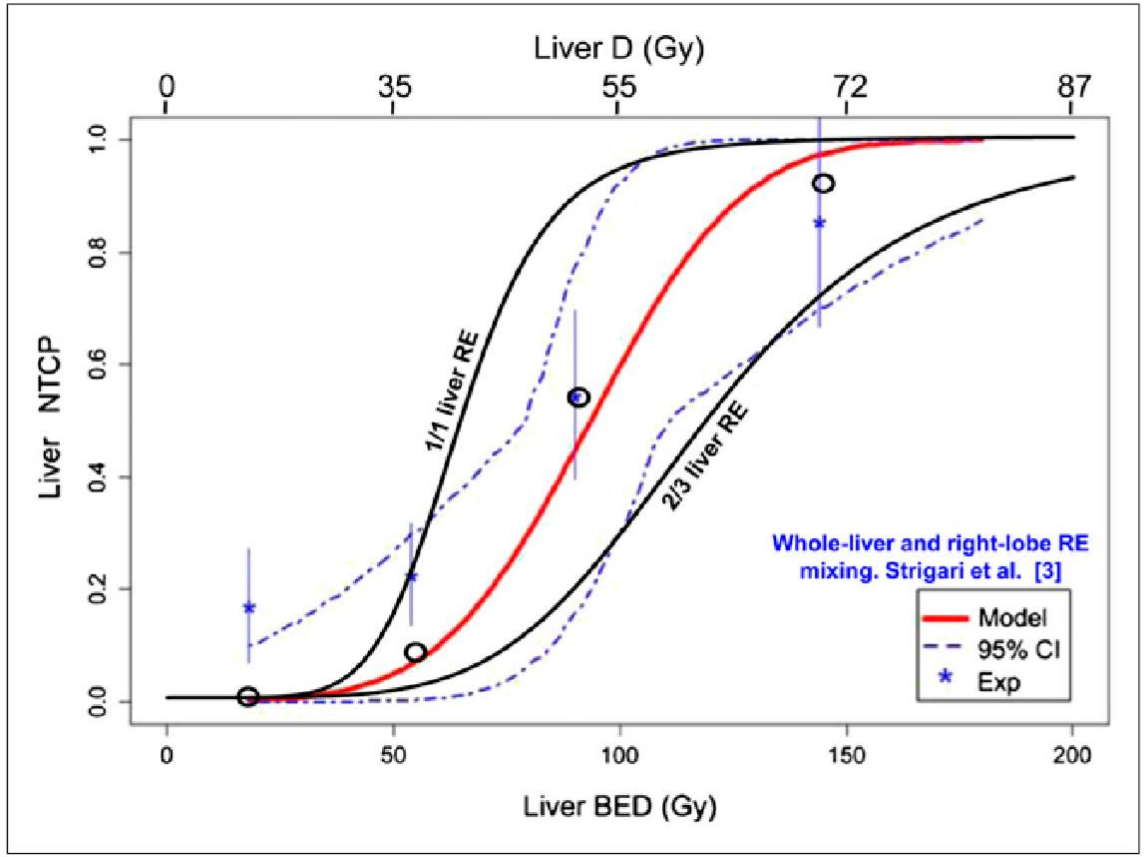
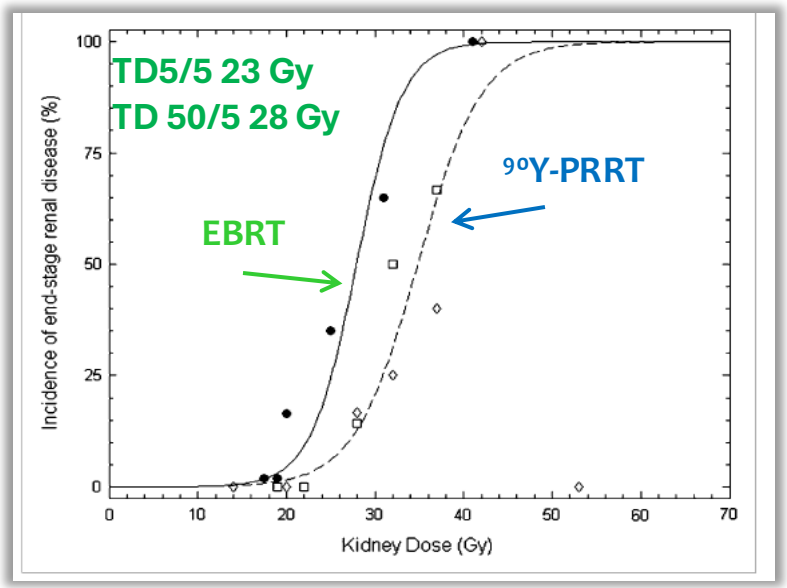
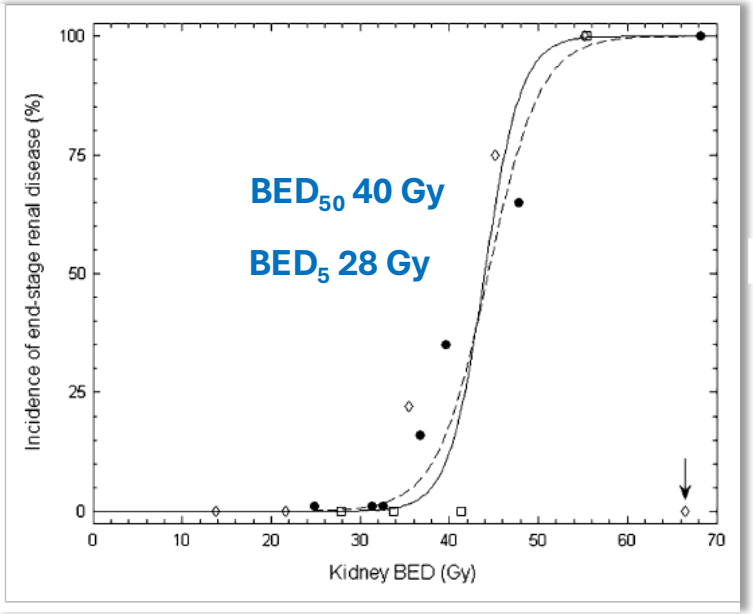


FIGURE 1. NTCP computation scheme. (Top) NTCP computation using simulated lobule dos distribution obtained from synthetic arterial tree. (Bottom) Potential individualization of lobu dose distribution derived from difference between simulated and patient voxel ^{90}Y biodistributio ^{90}Y biodistribution was computed from synthetic arterial tree convolved with PET resolution t allow its comparison with typical ^{90}Y time-of-flight PET imaging of patient after glass microsphe radioembolization not crossing tumors (both for delivered dose of 120 Gy to liver).



Kidneys Dose - renal toxicity: correlations found in ^{90}Y-PRRT





The higher non-uniformity of ^{177}Lu should mitigate the renal burden

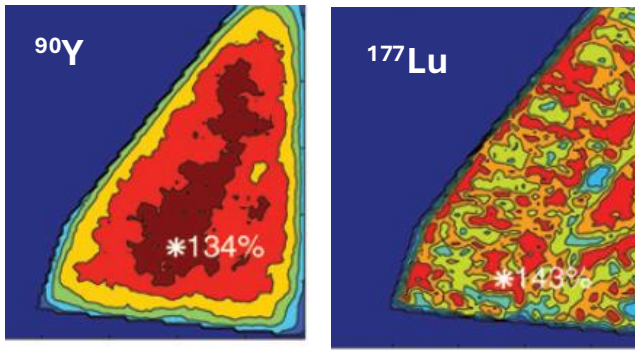
→ **higher tolerability of ^{177}Lu vs.^{90}Y**

→ **for the same mean dose**

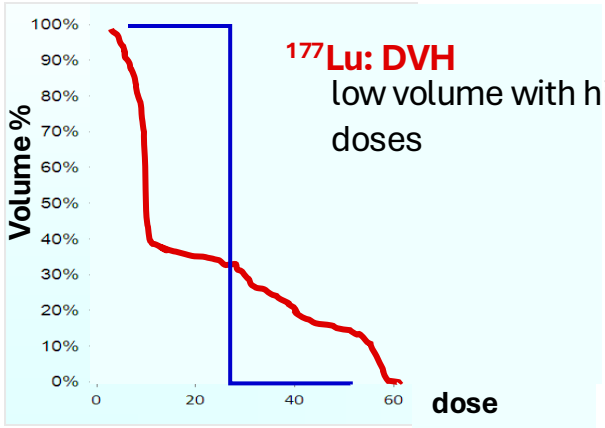
Subsequently confirmed by clinical data.

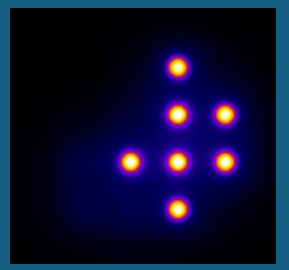
doi: 10.1016/0360-3016(91)90171-y.
doi: 10.2967/jnumed.108.053173

Dose distribution in renal cortex from autoradiography



Konijnenmerg M et al, JNM 2007; Wessels et al, 2008.

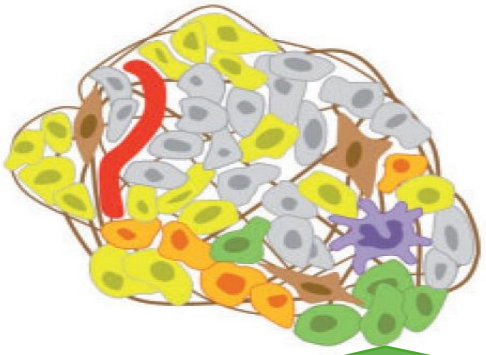




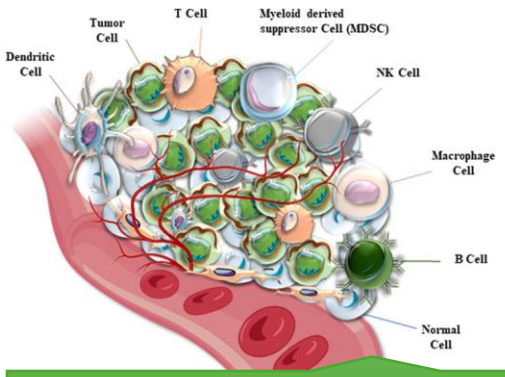
- **BT**
- **Lattice/GRID/microbeams**

→ **higher tolerability**

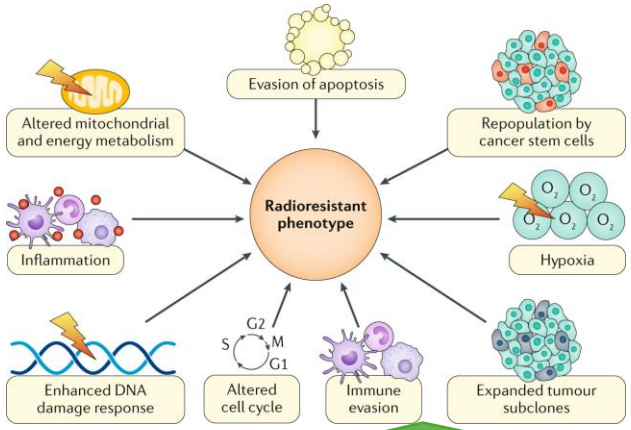
Current Challenges in Radionuclide Therapies



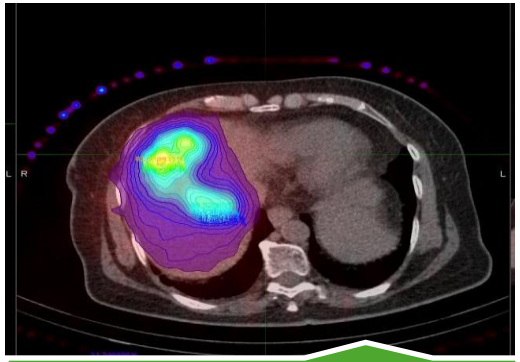
Tumour Heterogeneity



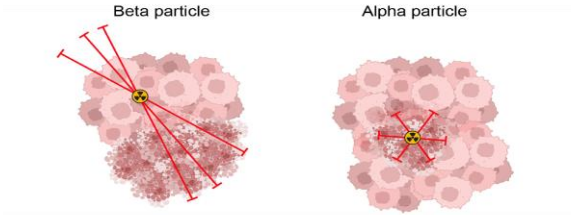
Tumour microenviroment



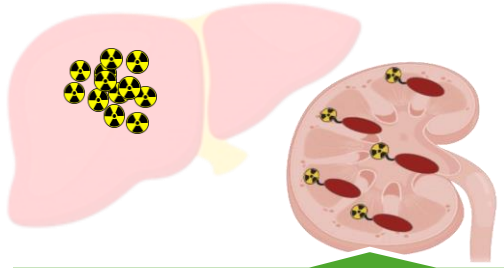
Tumor radiosensitivity/ radioresistance



Activity distribution heterogeneity



Radionuclide delivery



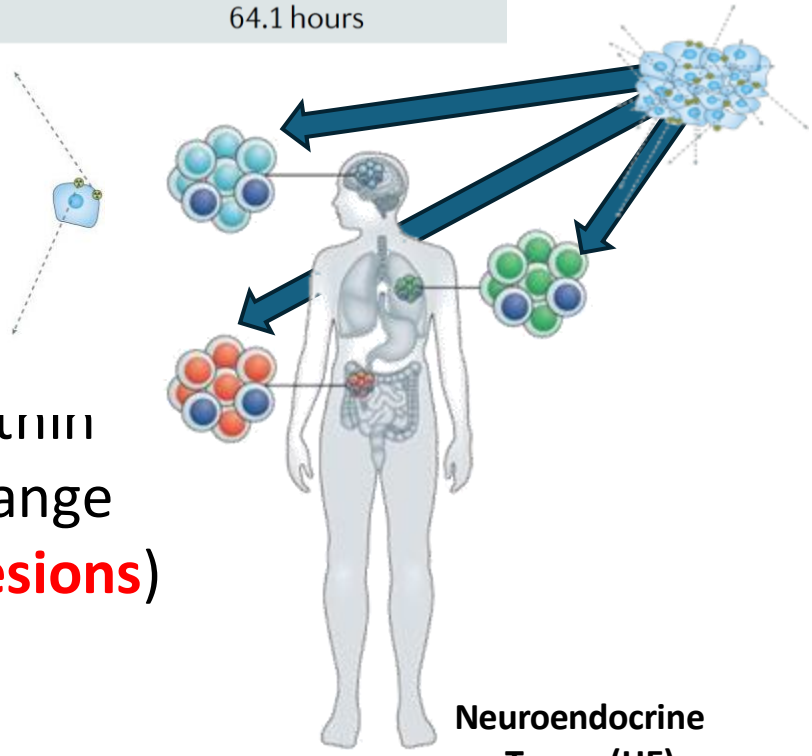
Geometric, PK-PD features

Rationale for Combining radionuclides

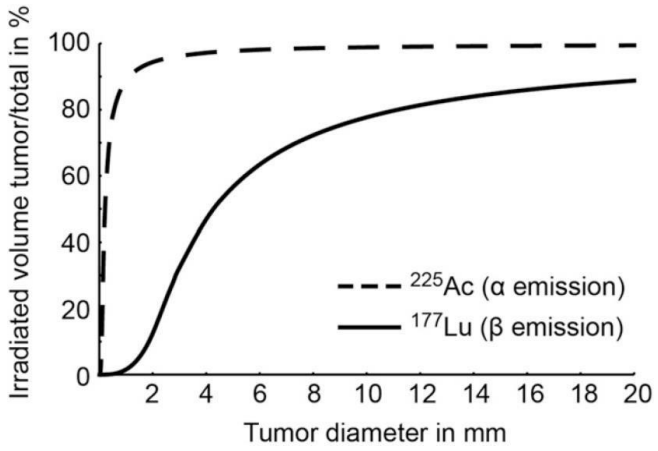
Dual Targeting

ALPHA VERSUS BETA RADIATION: MICRODOSIMETRY

Radionuclide	Therapeutic emission	Approximate emission range in tissue (mm)	Radionuclide half-life
Actinium-225	α	0.05–0.08	10.0 days
Lutetium-177	β^-	0.62	6.6 days
Yttrium-90	β^-	5.30	64.1 hours



Micrometastases



Tumor Heterogeneity

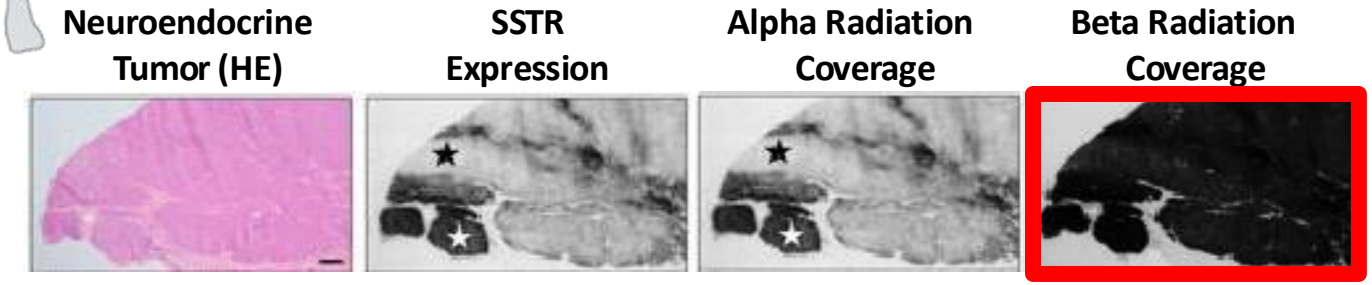
Pro Alpha?

Cytotoxicity within cell diameter range (**target small lesions**)

Pro Beta?

Cytotoxicity within tissue range (**target heterogeneity**)

RBE matters



Courtesy of Daniela Oprea-Lager

Sgouros et al. Nature Reviews | Drug Discovery Volume 19 | September 2020

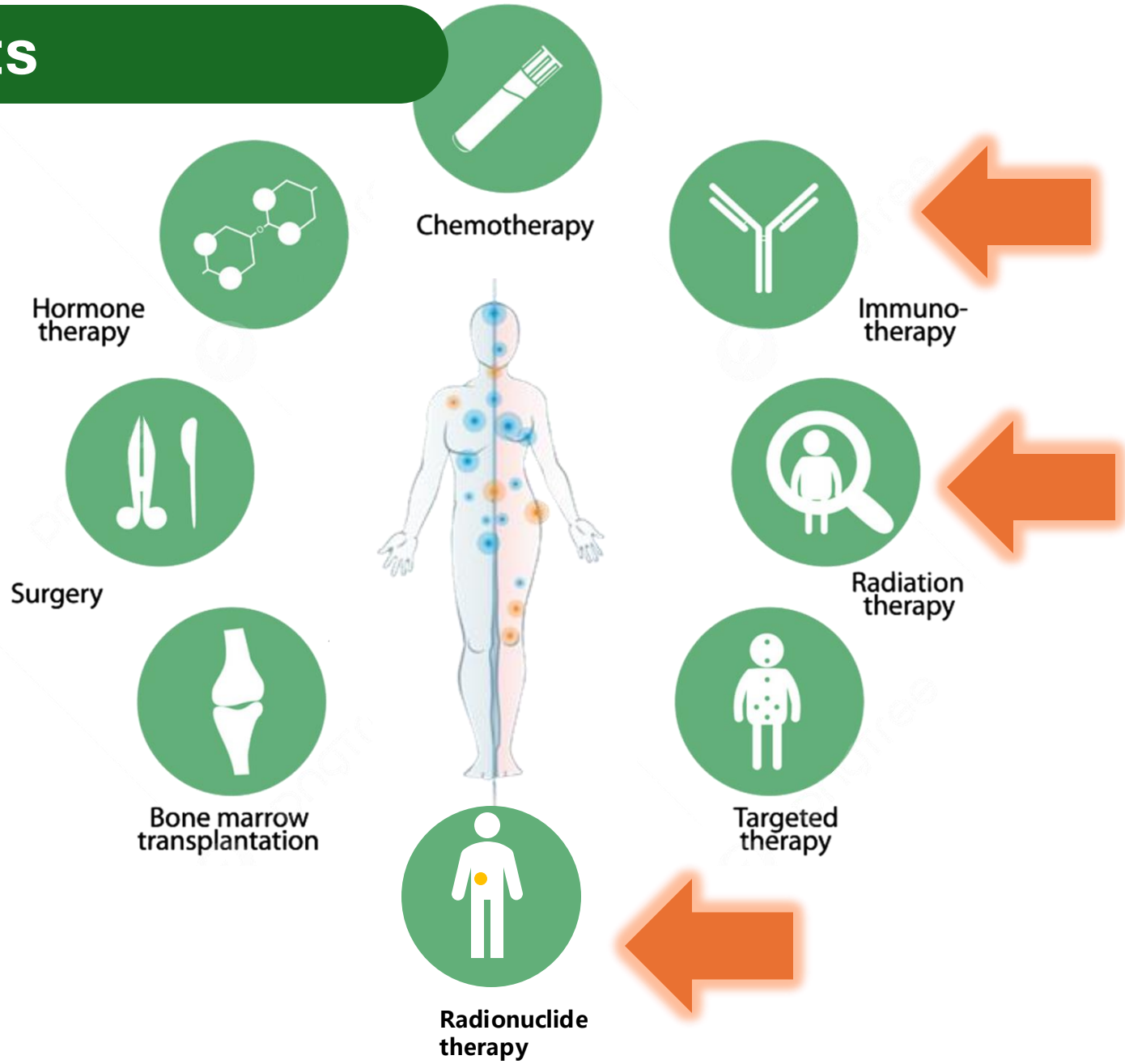
Fendler et al. J Nucl Med. 2017 Nov;58(11):1709-1710.

04 Combined treatments

Tumor recurrence

Aggressive disease

Plan higher doses or combined strategies



Advances in Radiation Oncology (2021) 6, 100617

How to move on ?

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in radiation oncology
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Scientific Article

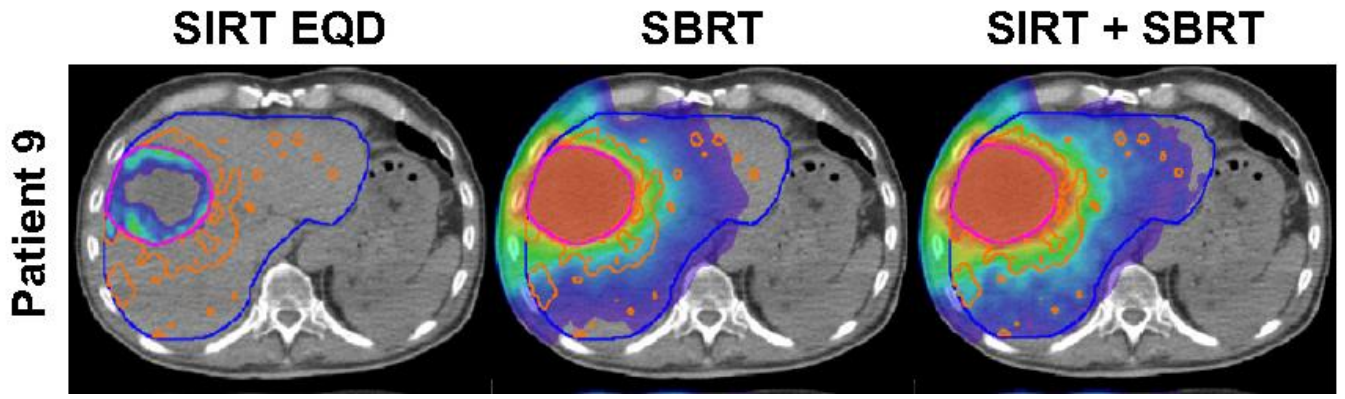
Stereotactic Inverse Dose Planning After Yttrium-90 Selective Internal Radiation Therapy in Hepatocellular Cancer

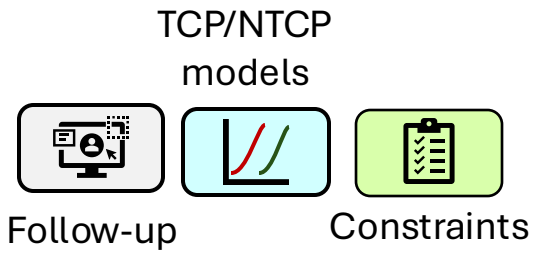
Elliot Abbott, DPhil, MSc,[a] Robert Steve Young, MD,[b] Caroline Hale,[c] Kimberly Mitchell, BS, CMD,[c] Nadia Falzone, PhD,[a] Katherine A. Vallis, MBBS, PhD, MRCP, FRCR, FRCPC,[a,1] and Andrew Kennedy, MD, FACRO[c,*,1]

[a]*Oxford Institute for Radiation Oncology, Department of Oncology, Oxford University, Oxford, United Kingdom;* [b]*Radiology Alliance, Centennial Medical Center, Nashville, Tennessee; and* [c]*Sarah Cannon Research Institute, Nashville, Tennessee*

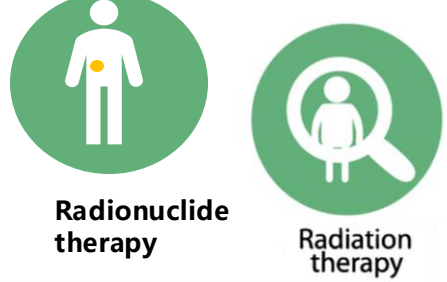
Treatment with both **EBRT** and **SIRT** can be given safely to patients with HCC.

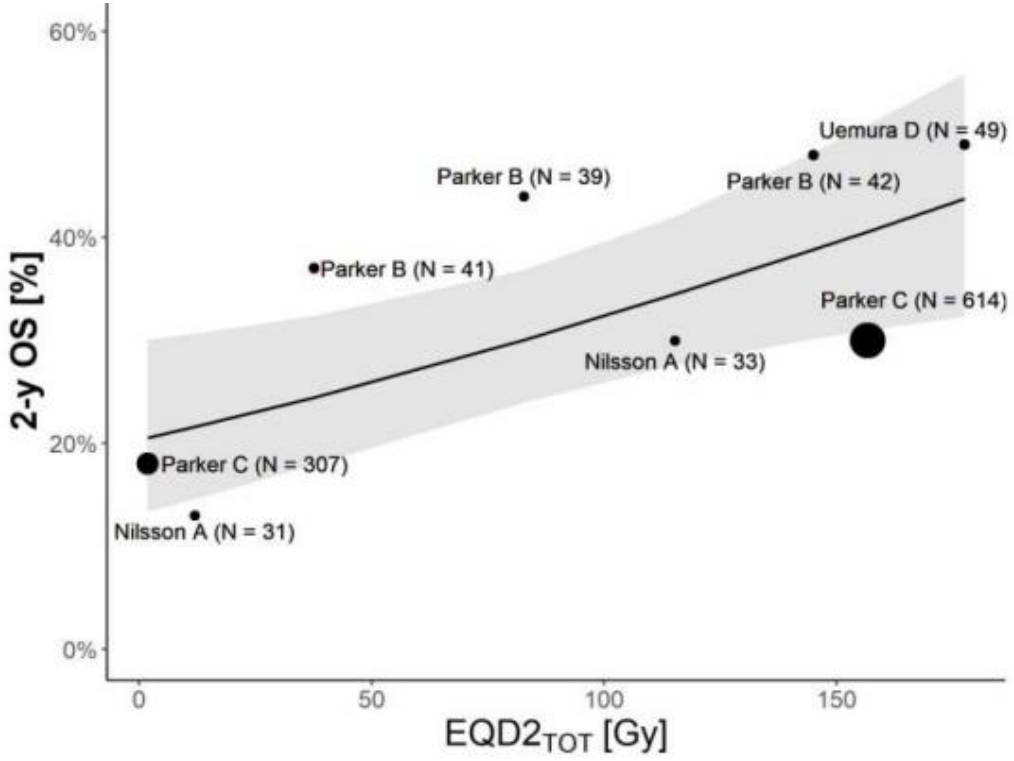
The **BED** and EQD concepts should be used in combined dosimetry to account for the differing radiobiological effects of EBRT and SIRT.

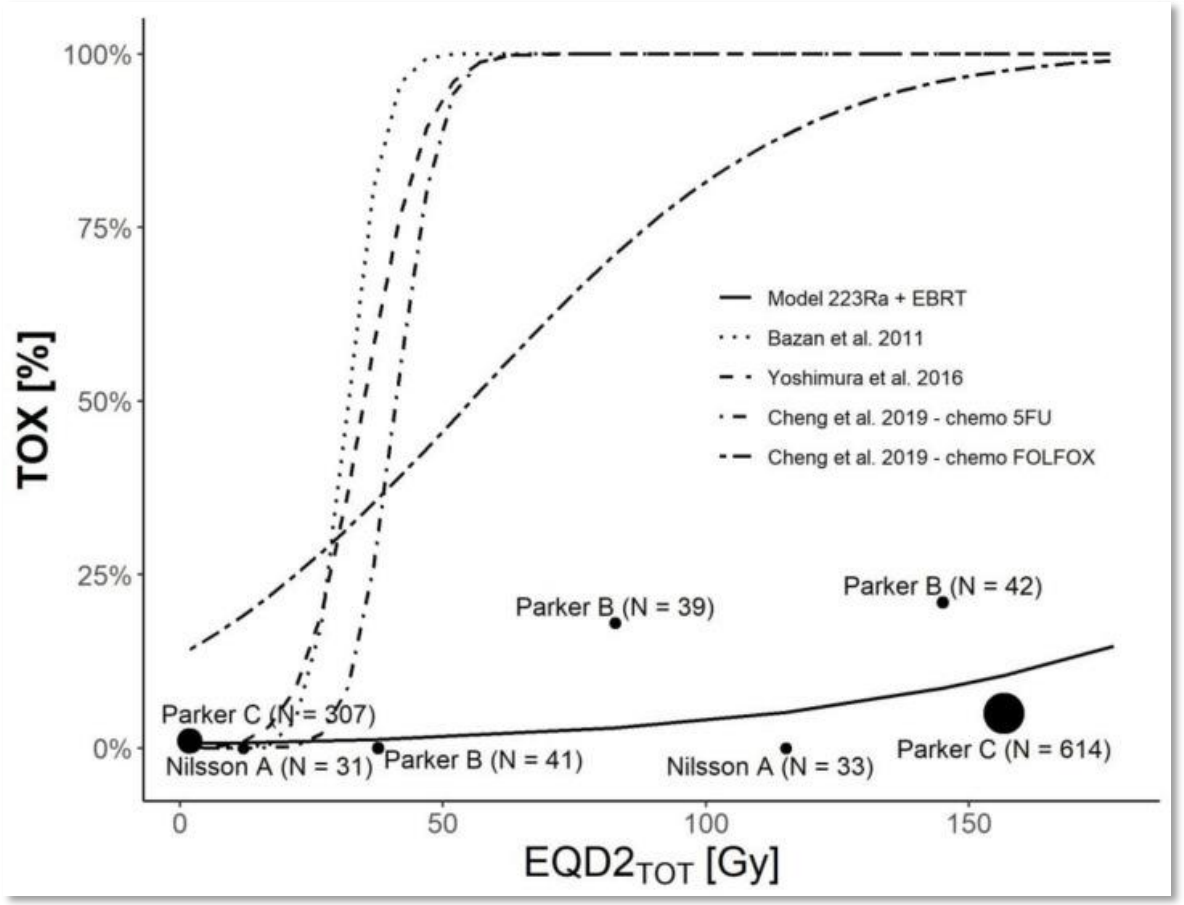




Alpha-Emitter Radiopharmaceuticals and EBRT: A Radiobiological Model for the Combined Treatment







Logistic regression model for 2-year **overall survival (2y-OS)** and **toxicity** rate (TOX), i.e., neutropenia
EBRT in combination with Ra223- Xofigo

Sarnelli A et al. Cancers (Basel). 2022

Immunotherapy + TARE

Enhancing Efficacy

Combination of radionuclides with other therapies (e.g., immunotherapy) can overcome resistance and improve tumor control.

May 2024

- Systemic treatment *Atezolizumab-Bevacizumab*

June 2024

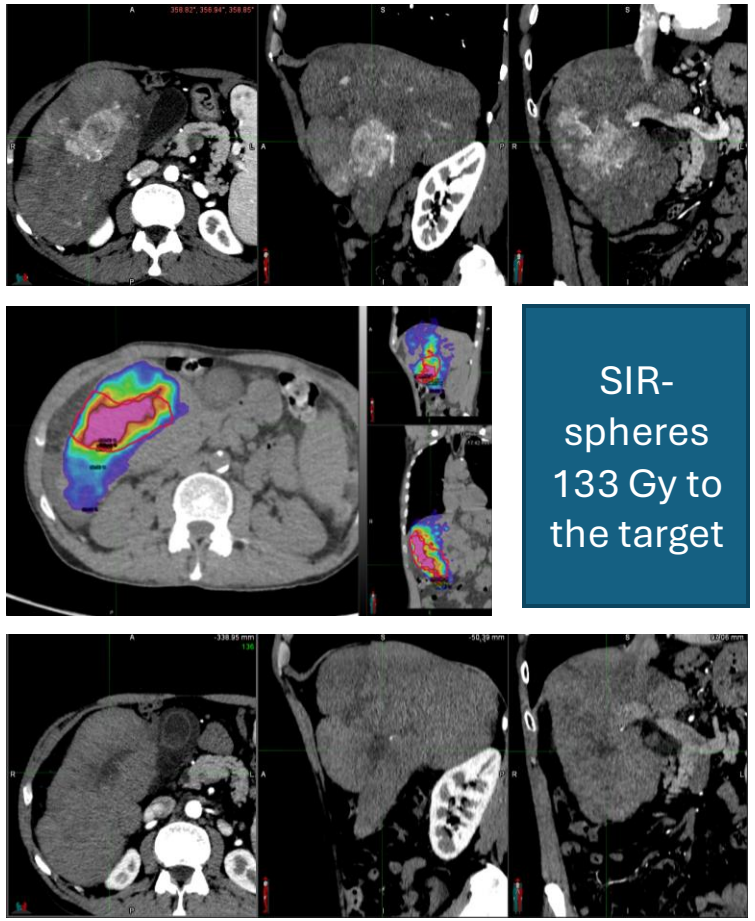
- SIRT treatment

August 2024

- Systemic treatment *Atezolizumab-Bevacizumab*

October 2024

- Complete response



Pre-TARE

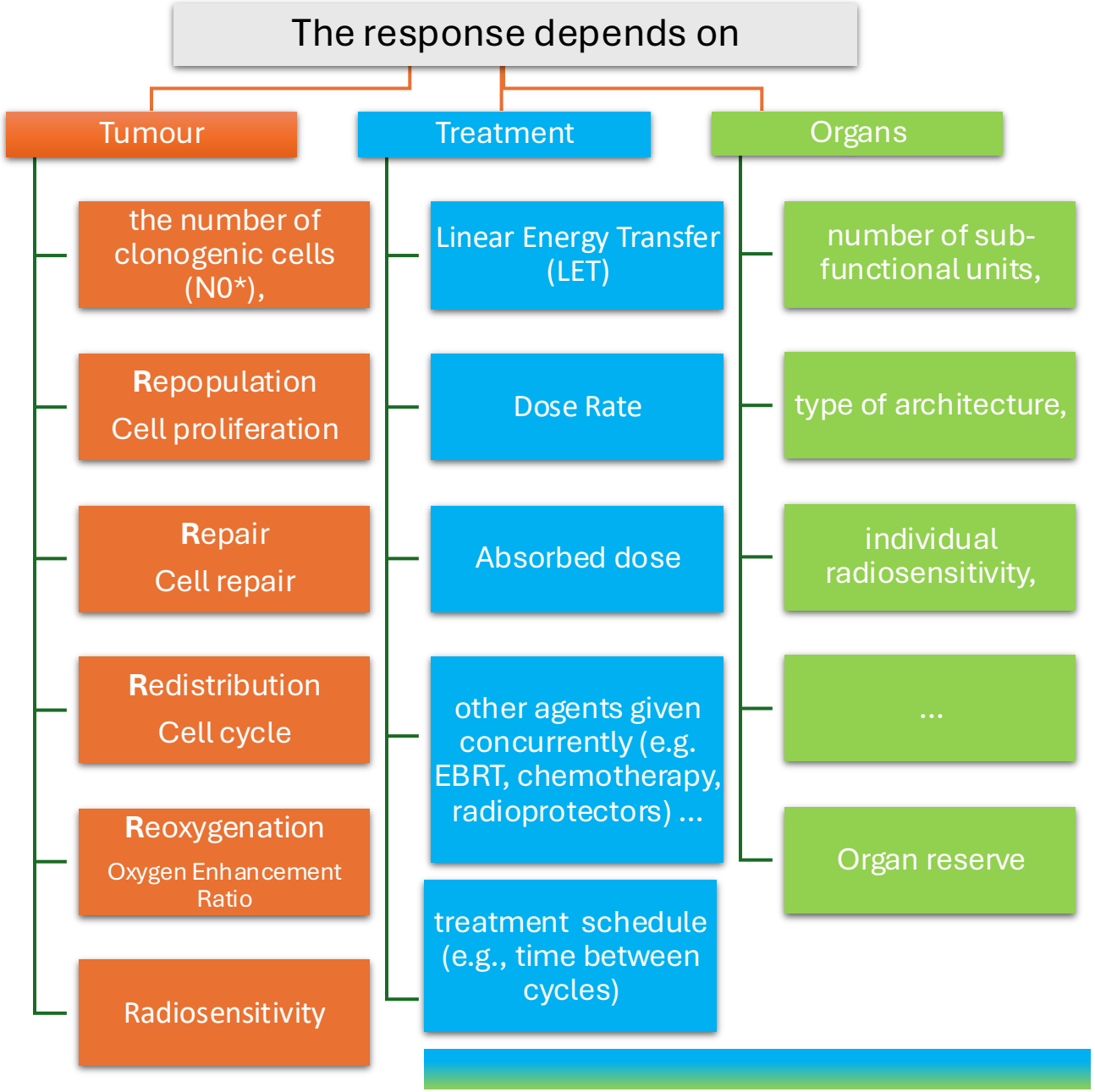
SIR-spheres 133 Gy to the target

Male,
58 years,
Multifocal HCC,
Right lobe

6 mos FUp

IRCCS AUOBo, Italy

Radiobiology is complex

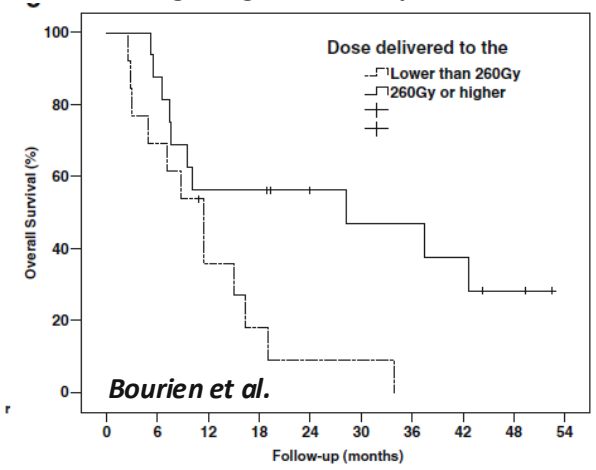


TCP = tumor control probability

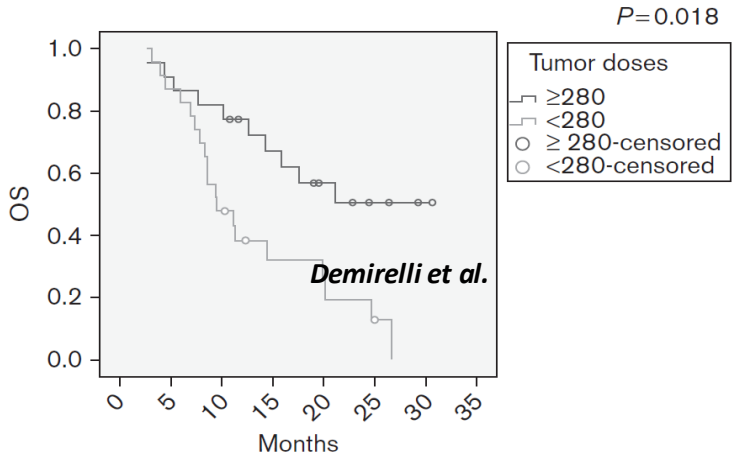
NTCP = normal tissue complication probability

Dose thresholds & Overall Survival

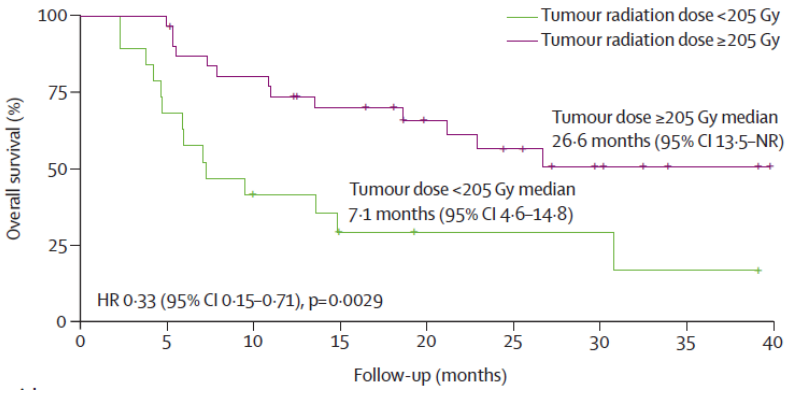
Yttrium-90 glass microspheres radioembolization (RE) for biliary tract cancer: a large single-center experience



Evaluation of factors affecting tumor response and survival in patients with primary and metastatic liver cancer treated with microspheres



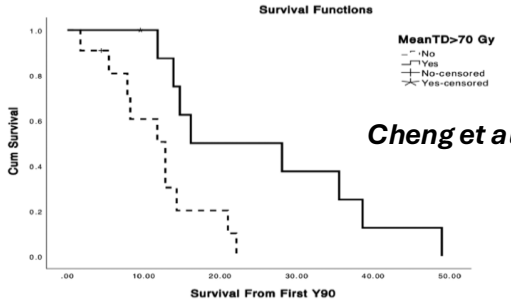
DOSISPHERE-01 ***Garin et al.***



The planning impacts the Overall Survival
26.6 months vs 9.9 (SARAH) or 11.3 (SIRveNIB trials)

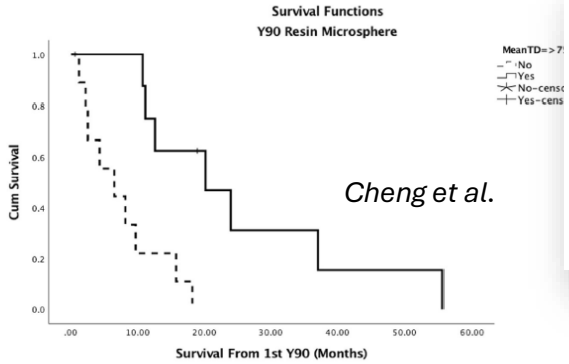
Original article

Yttrium-90 dosimetry and implications on tumour response and survival after radioembolisation of chemo-refractory hepatic metastases from breast cancer



in tumour dose >70 Gy experienced a median OS of 16.1 months vs. 12.8 months for those who did not (P=0.008). OS, overall

Determination of Tumor Dose Response Thresholds in Patients with Chemorefractory Intrahepatic Cholangiocarcinoma Treated with Resin and Glass-based Y90 Radioembolization



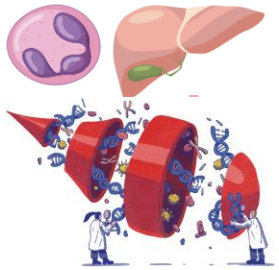
To 1000 Gy and back again: a systematic review on dose-response evaluation in selective internal radiation therapy for primary and secondary liver cancer

Joey Roosen [1] · Nienke J. M. Klaassen [1] · Lovisa E. L. Westlund Gotby [1] · Christiaan G. Overduin [1] · Marcel Verheij [2] · Mark W. Konijnenberg [1,3] · J. Frank W. Nijsen [1]

05 The optimal treatment
What we need to understand for proper therapy planning

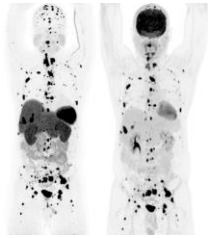
Patient presentation

Pharmacodynamic markers & liquid biopsy



Tumor target and behavior (selection, predictive markers)

Pre-therapeutic

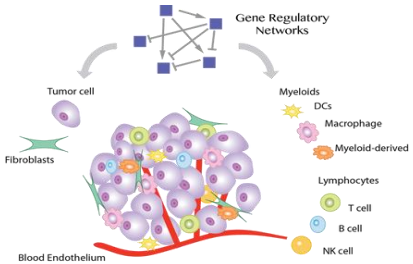


FDG-PET

XX

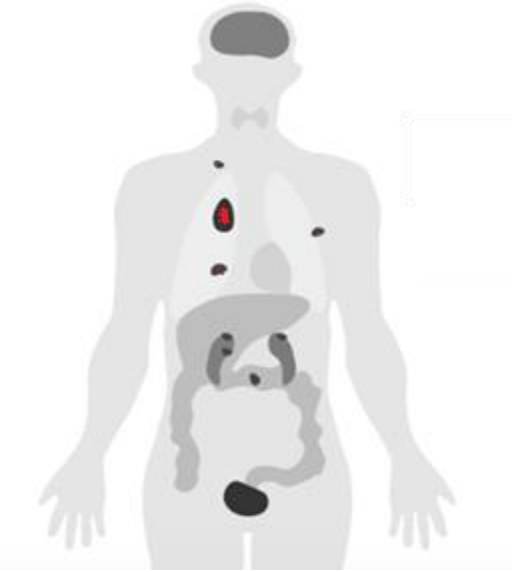
Genetic screening

Tumor microenvironnement & vasculature

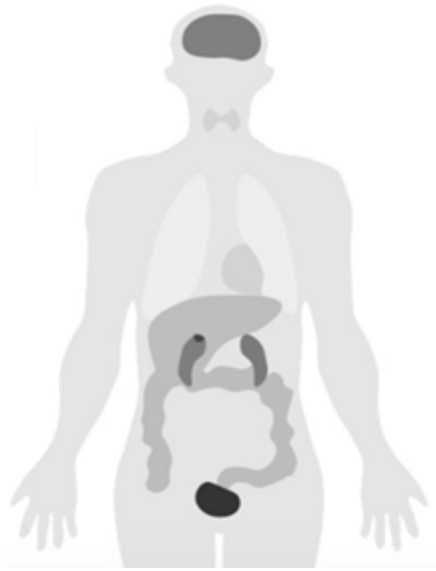


Molecular imaging

Treatment



Clinical goal



RATIONALE

WG 5. Clinical Translation – Strategies for treatment personalization/optimization

Lidia Strigari & Daniela E. Oprea-Lager

Thank you for the attention

lidia.strigari@aosp.bo.it