Modeling Impact of RT On the Immune Status of the Host

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Introduction

- Multiple evidences suggest that immune system plays an important role in RT
  - RT works better in immunocompetent mice than in immune-deficient mice
  - Overdose of RT reduce tumor control and increase metastasis
  - Radiation induced lymphopenia reduce survival
  - Abscopal effect in RT
- Modeling RT effect in immune system is important to optimize RT treatment and improve survival, especially for combination of RT with immunotherapy

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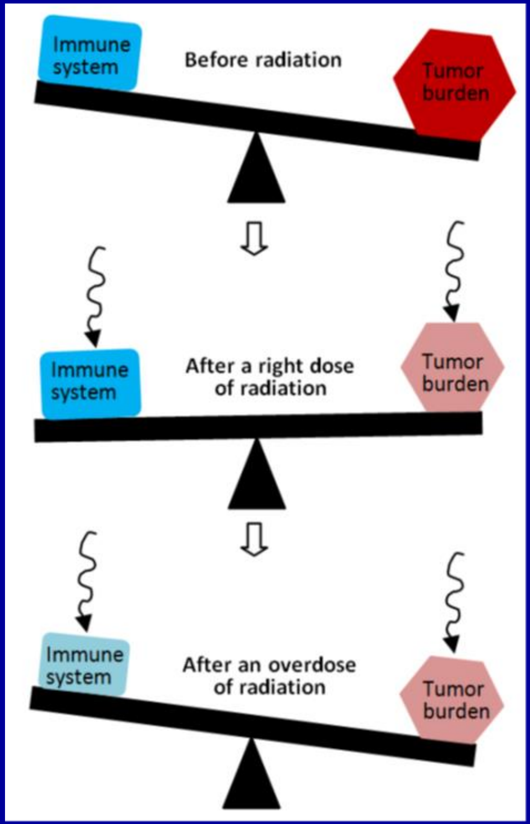
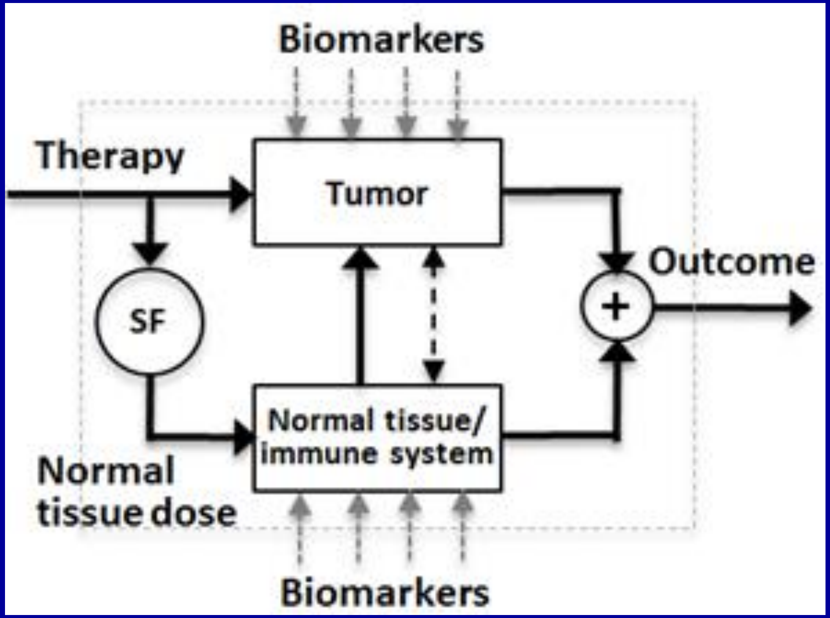
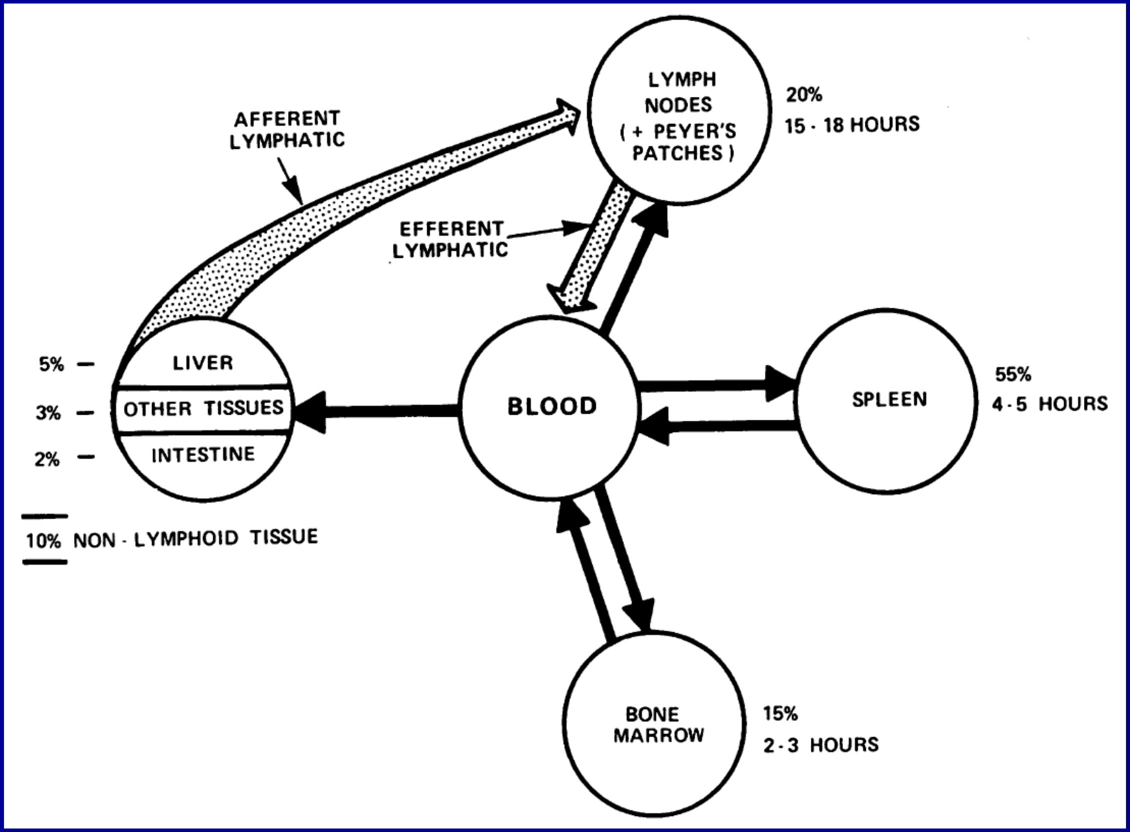
Modeling RT impact on immune system and treatment outcome





Composition of the immune system

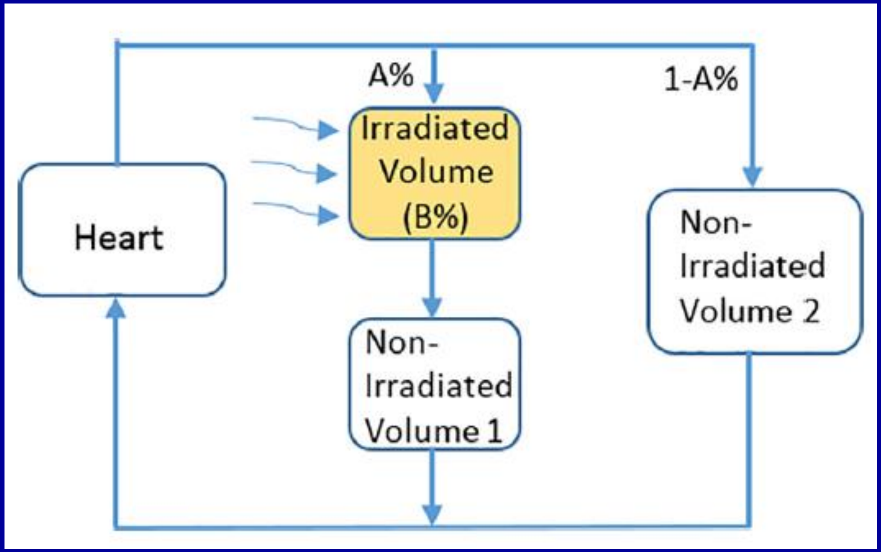


Ford WL. Lymphocytes. 3. Distribution. Distribution of lymphocytes in health. *J Clin Pathol Suppl (R Coll Pathol)*. 1979;13:63-69.

Modeling RT impact on immune system

- Modeling RT dose to the circulating immune cells in blood – Effective dose to immune cell in blood (EDIC)
  - Single organ contribution
  - Fractionation effect: using equivalent uniform dose
  - Combined effect from multiple blood containing organs
- Modeling RT dose to the entire immune system

Blood dose contribution from single organ



$$V\% = B\% + (A\% - B\%) * t/T$$

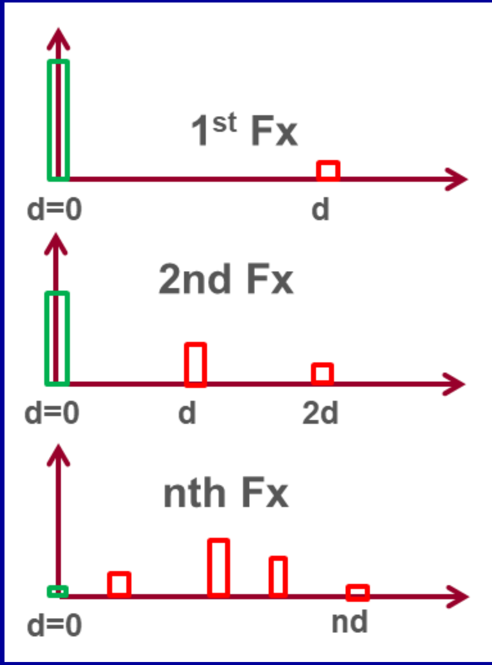
$$D = D_0 * \frac{B\%}{V\%}$$

- A%: % of blood current flow into the organ
- B%: % of blood volume within the organ
- T: Blood circulating period
- *t*: Irradiation time

Assuming t≤T. When t>T, same as multi-fraction effect

Multi-fraction effect

- Assuming V(i,j)(%) is the blood volume receiving a dose of d*j after *i*th Fx:
- 1st Fx: V(1,1)=V(%)= B(%)+(A-B)(%)*t/T, V(1,0)=1-V(1,1), $d_1=d=d_{MOD}*B/V$
- 2nd Fx: V(2,2)=V%*V(1,1), V(2,1)=V%*V(1,0) +(1-V%)*V(1,1), and V(2,0)=(1-V%)*V(1,0)
- *n*th Fx: V(n,n)=V%*V(n-1,1), V(n,n-1)=V%* V(n-1,n-2)+(1-V%)*V(n-1,n-1), …V(n,1)=V%*V(n-1,0)+(1-V%)*V(n-1,1), and V(n,0)=(1-V%)*V(n-1,0)



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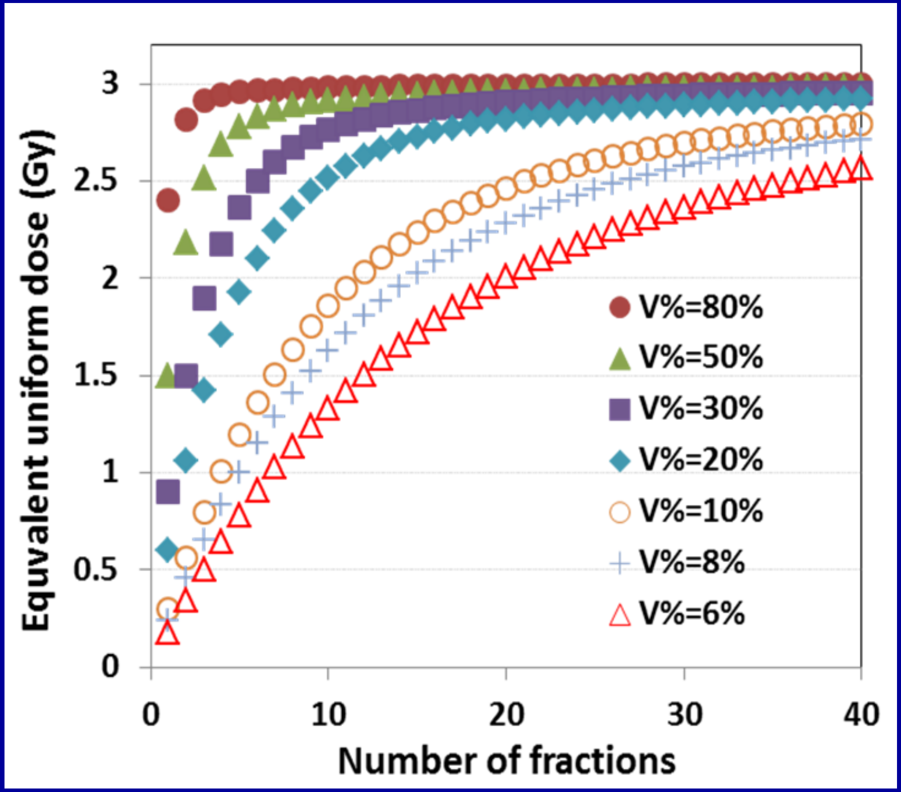
EDIC model

EUD to blood from a single organ



- When V% (=A%) > 20%, and n>25,

  EUD ~MOD*B%

- When V% ≤ 20%, n>15,

  $EUD \sim MOD*B\%*b*(n/45)^a$

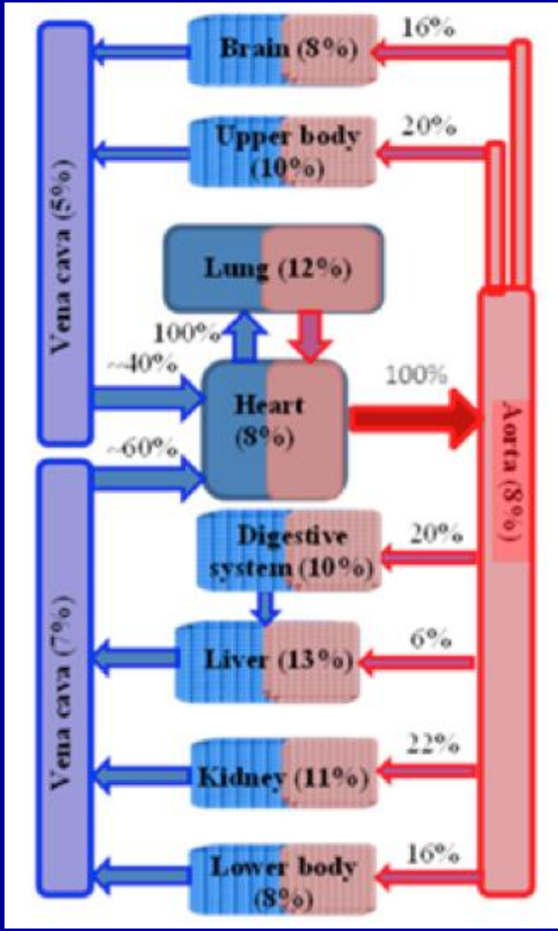
Where $a=0.87*\exp(-13.3*V\%)$

$b=1-0.0008*(V\%)^{-1.67}$

- When V%=5%, a=0.5, b=0.85

EDIC model: from multiple organs

Thoracic RT as an example



- EDIC is the sum of EUDs of multiple blood containing organs in an irradiated region
- Thoracic RT as an example: related organs include lungs, heart, large vessels, and small vessels/capillaries in other organs
- Integral total dose (ITD) to approximate the dose to large vessels and small vessels.
- A%=50%, 100%, 30-60%, 5% respectively for the 4 organs
- B%=12%, 8%, 45%*V/V_0, 35%*V/V_0 correspondently

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EDIC model for thoracic RT

$$EDIC = 0.12 * MLD + 0.08 * MHD + \left[0.45 + 0.35 * 0.85 * \left(\frac{n}{45}\right)^{1/2}\right] * \frac{ITD}{62 * 10^3}$$

Association of EDIC with survival

- Stage-III NSCLC
  - Jin et al. RTOG-0617 (456 patients)
  - Ladbury et al. University of Colorado (117 patients)
- Esophageal cancer treated with concurrent chemoradiotherapy
  - Xu et al. MD Anderson Cancer Center (488 patients)
  - So et al. Hong Kong University (92 patients, 91 stage-III, 1 stage-II)

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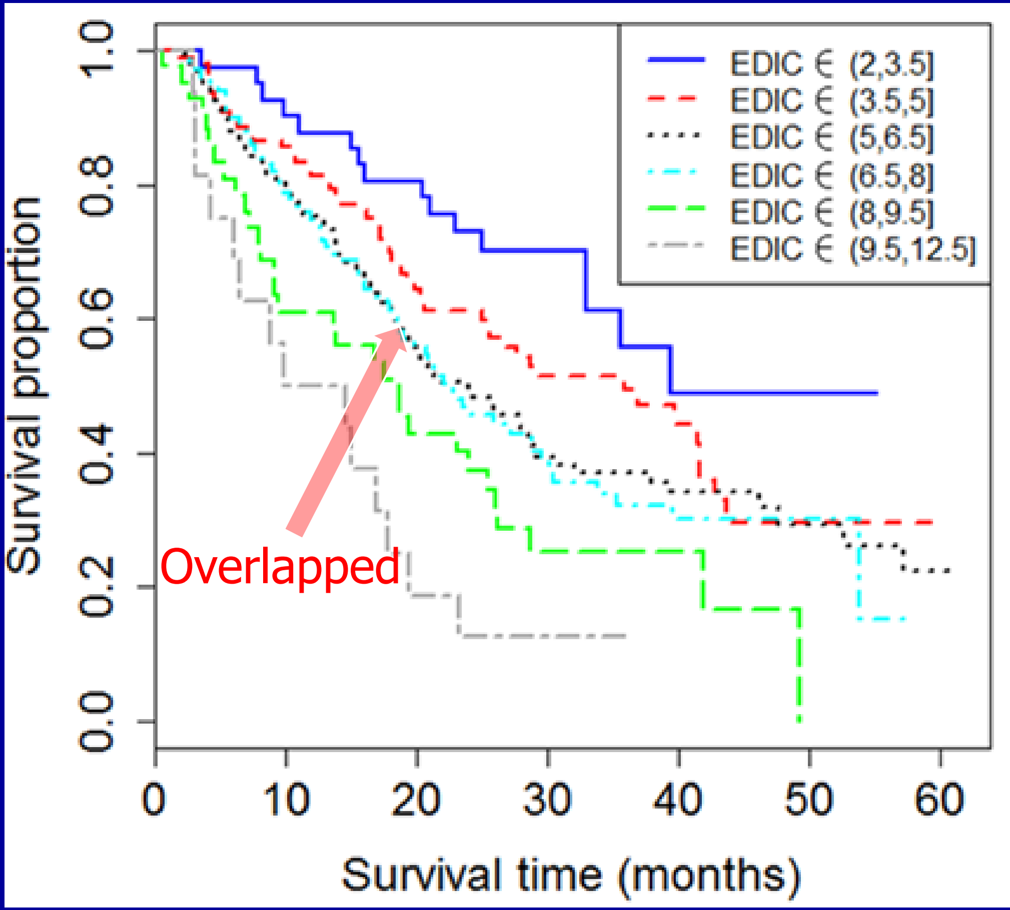
RTOG-0617



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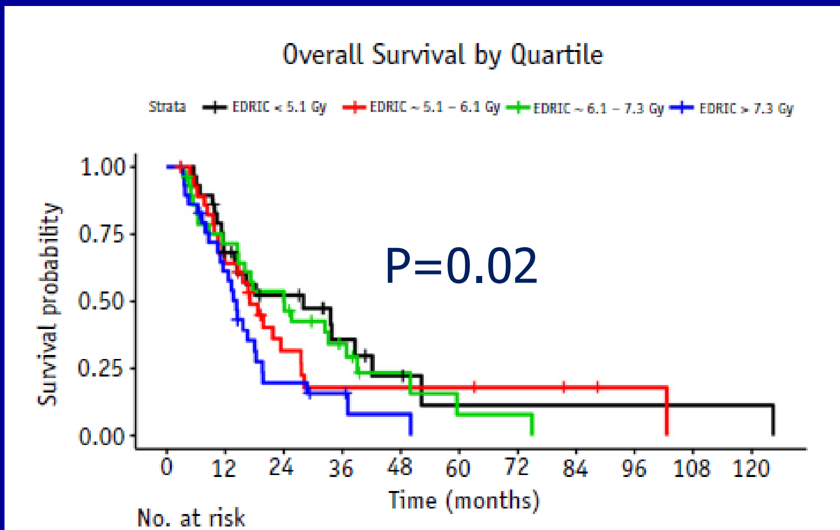
University of Colorado Data

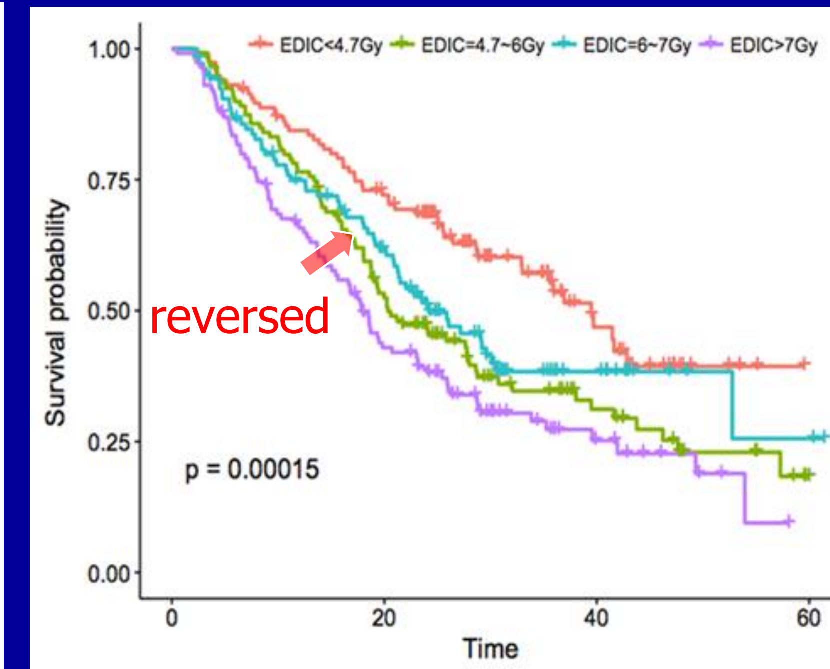
Colorado University



No. at risk

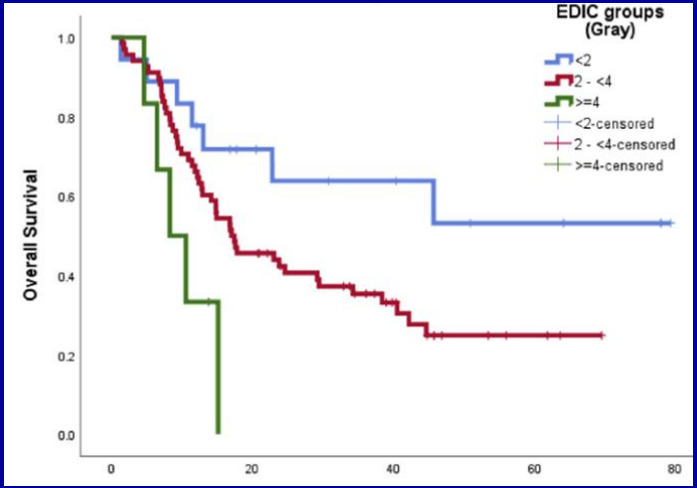
EDRIC < 5.1 Gy	30	18	12	6	3	1	1	1	1	1	1
EDRIC ~ 5.1 – 6.1 Gy	29	18	7	4	4	4	3	2	1	0	0
EDRIC ~ 6.1 – 7.3 Gy	29	20	15	7	3	1	1	0	0	0	0
EDRIC > 7.3 Gy	29	17	5	3	1	0	0	0	0	0	0

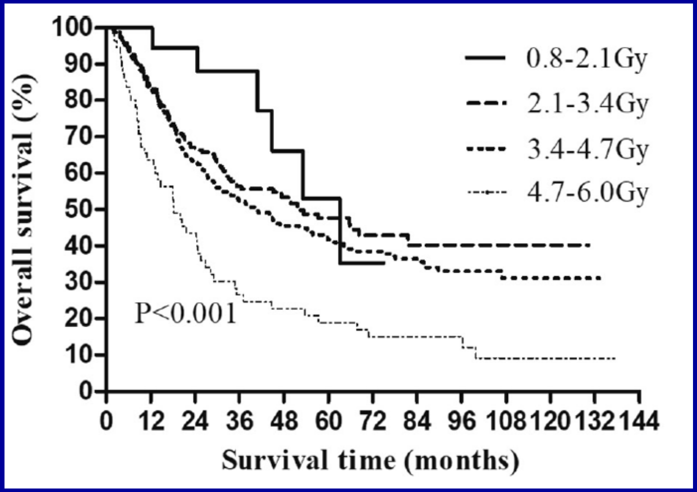
RTOG-0617



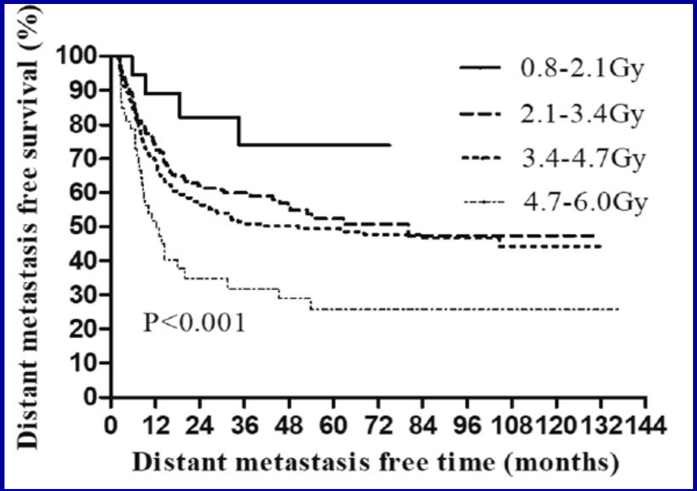
Ladbury CJ et al. Impact of Radiation Dose to the Host Immune System on Tumor Control and Survival for Stage III Non-Small Cell Lung Cancer Treated with Definitive Radiation Therapy. *Int J Radiat Oncol Biol Phys*. 2019;105(2):346-355.

Esophageal cancer: Hong-Kong U and MD Anderson results



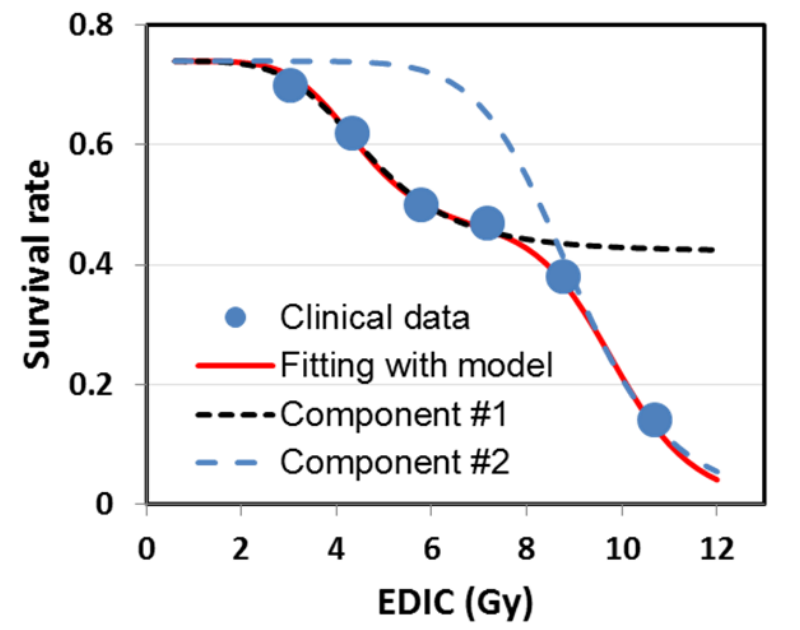


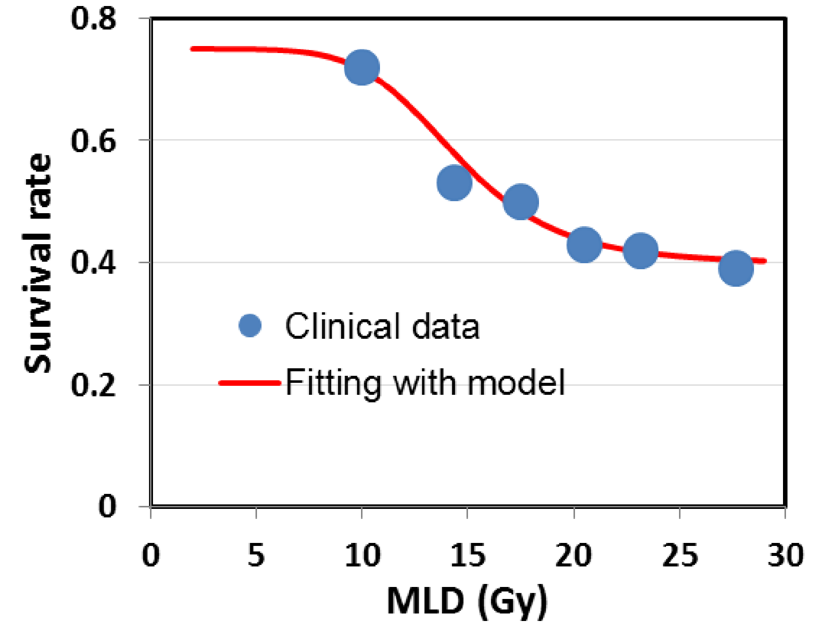
Hong Kong U: So TH, et al. Advances in Radiation Oncology (2020) (in press).



MD Anderson:
Xu C et al. Radiother Oncol. 2020;146:180-186.

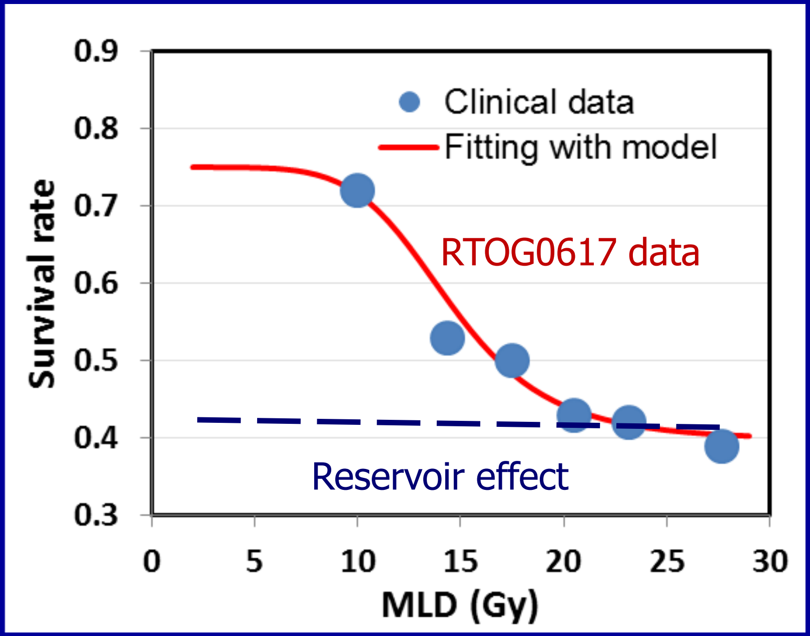
Survival-EDIC Dose response

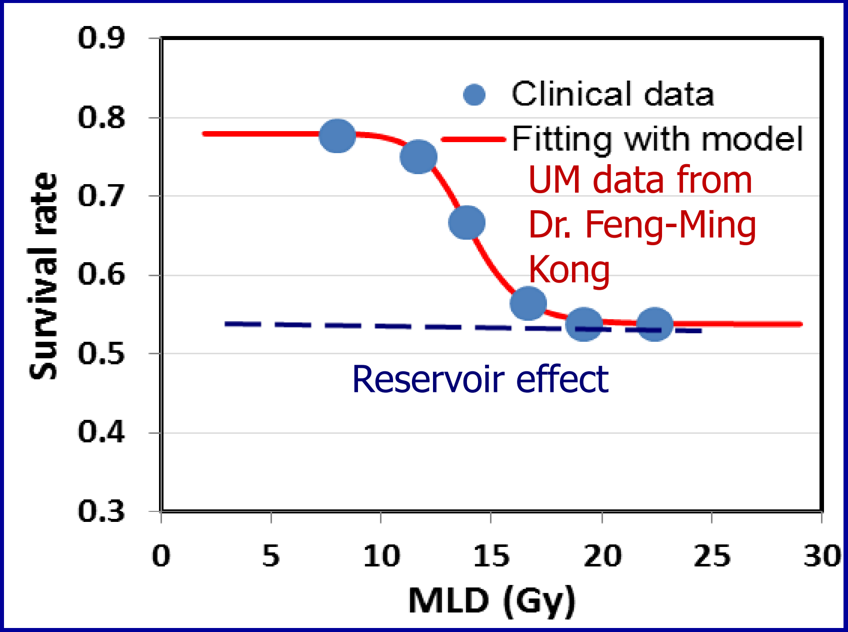




- Two components in the EDIC response curve! Contribution from lymphatic stations in lung or reservoir effect?

Similar MLD dose responses



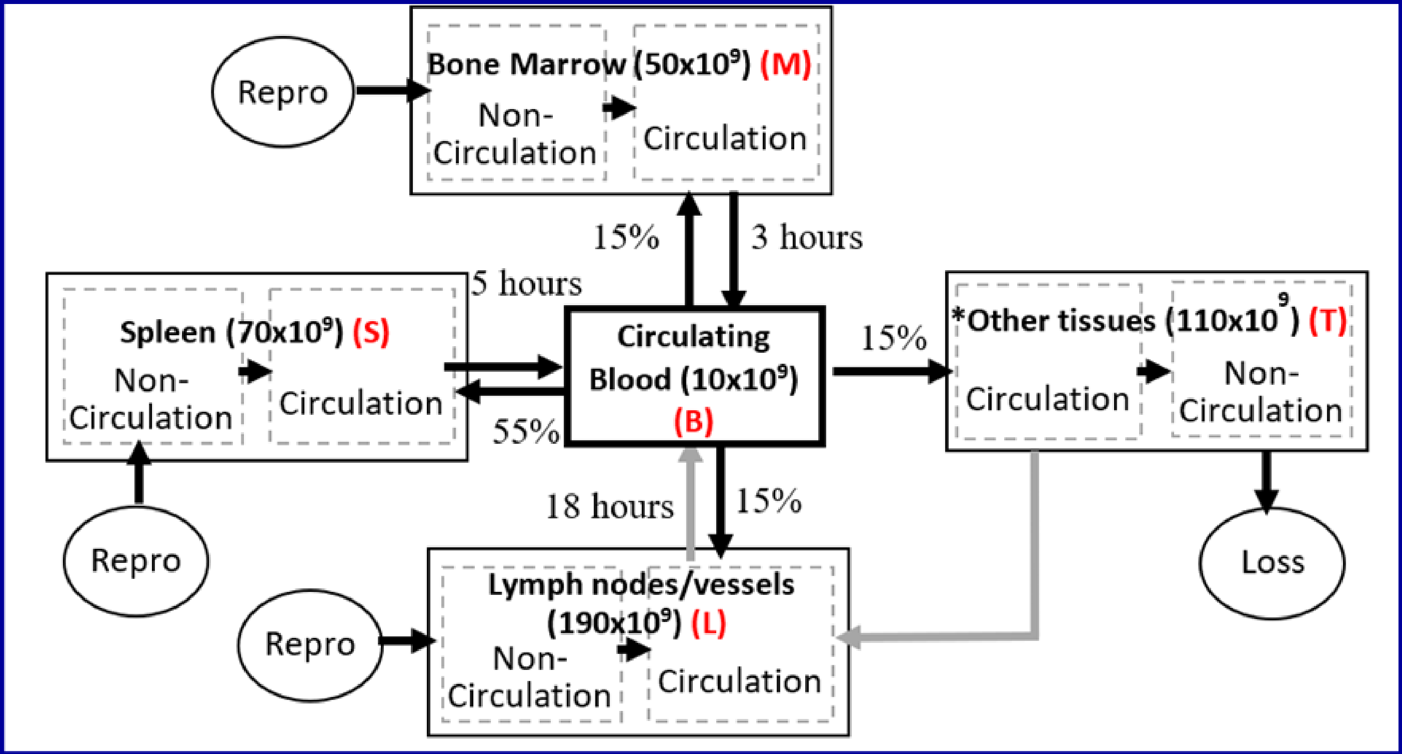


- Similar dose responses for MLD with D_{50}~13-14 Gy for both RTOG-0617 and UM data

Modeling RT effect on entire immune system

- Doses to all 5 compartments are calculated from DVHs of a plan
- Lymphocyte transportations between compartments are modeled using differential equations
- Lymphocyte killing at each compartment at each fraction is directly calculated using LQ-model
- Radiosensitivity and Reproductivity rate are used as fitting parameters in the model
- We have tested the model by comparing it with weekly measured absolute lymphocyte counts (ALCs) for 51 abdominal cancer patients

Modeling RT dose to the entire immune system



Lymphocyte dynamical model

$$\frac{dN_{MN}(t)}{\mathrm{dt}} = (k_R - k_{MN-MC}) \cdot N_{MN}(t) - \frac{\Delta N_{MN}(t,D)}{\Delta t} \qquad \text{(1a)}$$

$$\frac{dN_{SN}(t)}{\mathrm{dt}} = (k_R - k_{SN-SC}) \cdot N_{SN}(t) - \frac{\Delta N_{SN}(t,D)}{\Delta t} \qquad \text{(1b)}$$

$$\frac{dN_{LN}(t)}{\mathrm{dt}} = (k_R - k_{LN-LC}) \cdot N_{LN}(t) - \frac{\Delta N_{LN}(t,D)}{\Delta t} \qquad \text{(1c)}$$

$$\frac{dN_{TN}(t)}{\mathrm{dt}} = k_{TC-TN} \cdot N_{TC}(t) - k_L \cdot N_{TN}(t) - \frac{\Delta N_{TC}(t,D)}{\Delta t} \qquad \text{(1d)}$$

$$\frac{dN_{MC}(t)}{\mathrm{dt}} = k_{MN-MC} \cdot N_{MN}(t) + k_{B-MC} \cdot N_B(t) - k_{MC-B} \cdot N_{MC}(t) - \frac{\Delta N_{MC}(t,D)}{\Delta t} \qquad \text{(1e)}$$

$$\frac{dN_{SC}(t)}{\mathrm{dt}} = k_{SN-SC} \cdot N_{SN}(t) + k_{B-SC} \cdot N_B(t) - k_{SC-B} \cdot N_{SC}(t) - \frac{\Delta N_{SC}(t,D)}{\Delta t} \qquad \text{(1f)}$$

$$\frac{dN_{LC}(t)}{\mathrm{dt}} = k_{LN-LC} \cdot N_{LN}(t) + k_{B-LC} \cdot N_B(t) + k_{TC-LC} \cdot N_{TC}(t) - k_{LC-B} \cdot N_{LC}(t) - \frac{\Delta N_{LC}(t,D)}{\Delta t} \qquad \text{(1g)}$$

$$\frac{dN_{TC}(t)}{\mathrm{dt}} = k_{B-TC} \cdot N_B(t) - (k_{TC-LC} - k_{TC-TN}) \cdot N_{TC}(t) - \frac{\Delta N_{TC}(t,D)}{\Delta t} \qquad \text{(1h)}$$

$$\frac{dN_B(t)}{dt} = k_{MC-B} \cdot N_{MC}(t) + k_{SC-B} \cdot N_{SC}(t) + k_{LC-B} \cdot N_{LC}(t) -$$

$$(k_{B-MC} + k_{B-SC} + k_{B-LC} + k_{B-TC}) \cdot N_B(t) - \frac{\Delta N_B(t,D)}{\Delta t} \qquad \text{(1i)}$$

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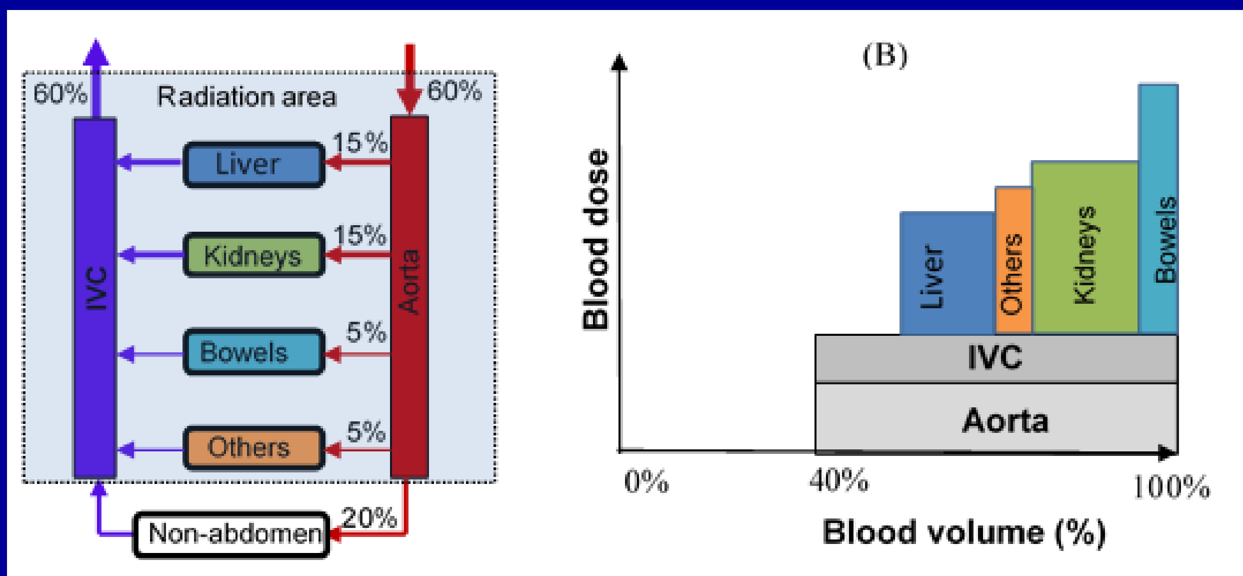
An example in abdominal irradiation

RT dose to circulating blood

$$V_j = p_2 + (p_1 - p_2)\times\frac{t}{T} = p1$$

$$d_j = MOD\times\left(\frac{p_2}{V_j}\right) = MOD\times\left(\frac{p_2}{p_1}\right)$$

V_j: Irradiated blood volume
d_j: Dose to the irradiated volume
P_1: Percentage cardiac output flowing through the organ
P_2: Percentage blood volume contained in an organ



Calculate number of lymphocytes killed by radiation

- For non-circulating lymphocytes in non-blood compartment I

$$\Delta N_I(t+\Delta t, d) = [N_I(t) - (1-b_I)\cdot N_I(0)]\cdot(1-e^{-\alpha\cdot d_I})\cdot \Delta t \cdot k_t \cdot e^{-k_t\cdot t}$$

- For circulating lymphocytes in non-blood compartment I

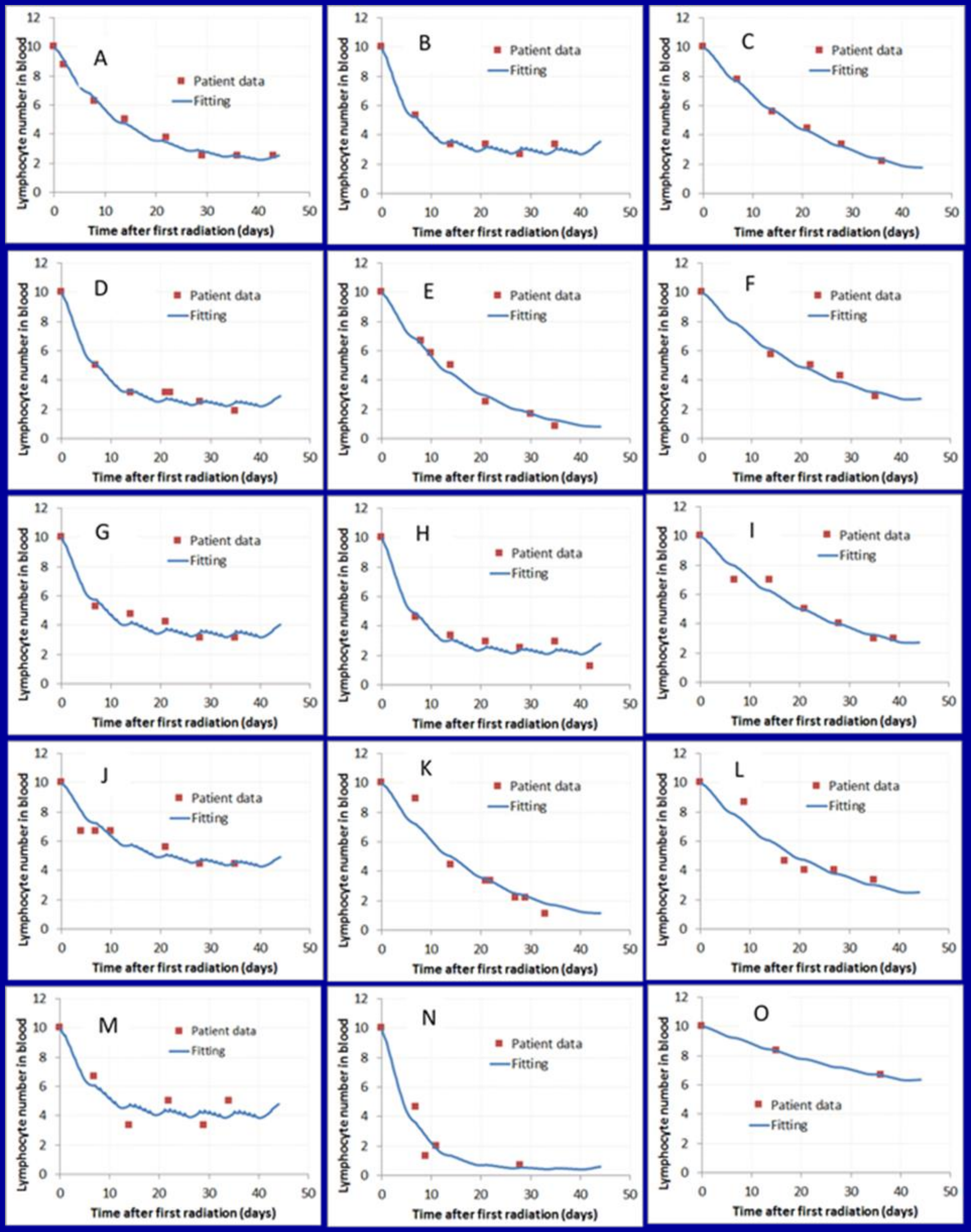
$$\Delta \mathrm{N}_I(t+\Delta t, d) = N_I(t)\cdot b_I\cdot(1-e^{-\alpha\cdot d_I})\cdot \Delta t \cdot k_t \cdot e^{-k_t\cdot t}$$

- For lymphocytes in the circulating blood

$$\Delta \mathrm{N}_{B-i}(t+\Delta t, d_i) = N_B(t)\cdot v_i\cdot(1-e^{-\alpha\cdot d_i})\cdot \Delta t \cdot k_t \cdot e^{-k_t\cdot t}$$

$$\Delta \mathrm{N}_B(t+\Delta t, d) = \sum_{i=1}^{6} \Delta N_{B-i}(t+\Delta t, d_i)$$

Fitting results



Perfect: SSE<0.5, 20 patients

Excellent: SSE~0.5-1.0, 14 patients

Good: SSE~1.0-2.0, 7 patients

Fair: SSE~2.0-4.0, 6 patients

Poor: SSE>4.0, 4 patients

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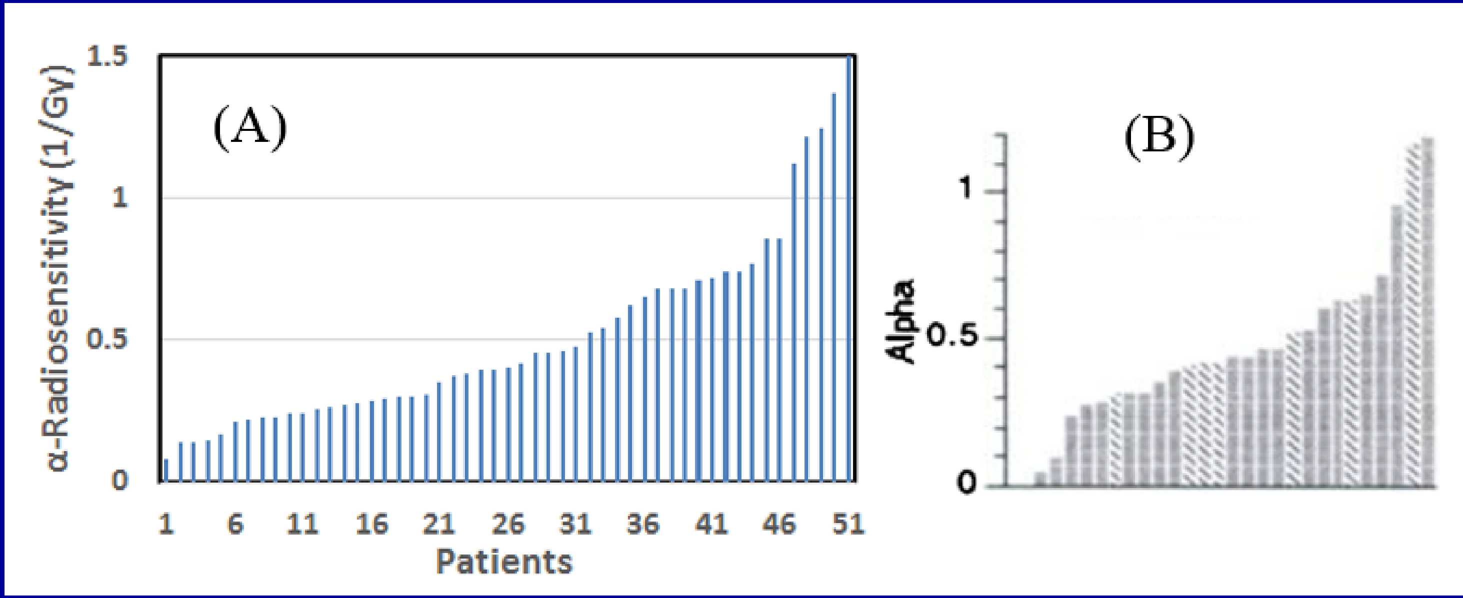
Comparison of *in vivo* estimated data with *in vitro* measured data in literature



In vitro data from 31 patients published 40 years ago by
Median radiosensitivity (α) =0.40 (1/Gy) in our 51 patients. It was 0.41 (1/Gy) from literature

Summary

- Radiation dose to immune cells in blood (EDIC) and to the entire immune system may be modeled using data from a treatment plan
- Four independent studies demonstrated that EDIC is significantly associated with overall survival
- Lymphocyte loss or lymphopenia may be associated with immune dose and radiosensitivity
- Individual immune radiosensitivity may be derived by modeling immune dose and comparing measured lymphocyte counts