Modeling Impact of RT On the Immune Status of the Host

Jian-Yue Jin, PhD

Radiation Oncology, Seidman Cancer Center, University Hospitals Cleveland Medical Center
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
Modeling RT impact on immune system and treatment outcome
Composition of the immune system

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

Assuming $t \leq T$. When $t > T$, same as multi-fraction effect

The diagram shows the flow of blood through an organ, with different volumes and fractions.

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

Mathematical equations:

\[ V_0 = B\% + (A\% - B\%) \times \frac{t}{T} \]

\[ D = D_0 \times \frac{B\%}{V_0} \]
Multi-fraction effect

- Assuming $V(i,j)(\%)$ is the blood volume receiving a dose of $d^j$ after $i$th Fx:
  - 1st Fx: $V(1,1)=V(\%) = B(\%) + (A-B)(\%)*t/T$, $V(1,0)=1-V(1,1)$, $d_1=d=d_{\text{MOD}}*B/V$
  - 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 $V(n,0)=(1-V\%)*V(n-1,0)$
EDIC model
EUD to blood from a single organ

- When $V\% = A\% > 20\%$, and $n > 25$,
  \[ EUD \sim MOD \times B\% \]
- When $V\% \leq 20\%$, $n > 15$,
  \[ EUD \sim MOD \times B\% \times b \times \left(\frac{n}{45}\right)^a \]
  Where
  \[ a = 0.87 \times \exp(-13.3 \times V\%) \]
  \[ b = 1 - 0.0008 \times (V\%)^{-1.67} \]
- 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.
EDIC model for thoracic RT

\[ EDIC = 0.12 \times MLD + 0.08 \times MHD + \]

\[ \left[ 0.45 + 0.35 \times 0.85 \times \left( \frac{n}{45} \right)^{1/2} \right] \times \frac{ITD}{62 \times 10^3} \]
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)
Esophageal cancer: Hong-Kong U and MD Anderson results


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 $D_{50} \sim 13-14$ 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

\[
\frac{dN_{MN}(t)}{dt} = (k_R - k_{MN-MC}) \cdot N_{MN}(t) - \frac{\Delta N_{MN}(t,D)}{\Delta t} \tag{1a}
\]

\[
\frac{dN_{SN}(t)}{dt} = (k_R - k_{SN-SC}) \cdot N_{SN}(t) - \frac{\Delta N_{SN}(t,D)}{\Delta t} \tag{1b}
\]

\[
\frac{dN_{LN}(t)}{dt} = (k_R - k_{LN-LC}) \cdot N_{LN}(t) - \frac{\Delta N_{LN}(t,D)}{\Delta t} \tag{1c}
\]

\[
\frac{dN_{TN}(t)}{dt} = k_{TC-TN} \cdot N_{TC}(t) - k_L \cdot N_{TN}(t) - \frac{\Delta N_{TC}(t,D)}{\Delta t} \tag{1d}
\]

\[
\frac{dN_{MC}(t)}{dt} = k_{MN-MC} \cdot N_{MN}(t) + k_{B-MC} \cdot N_{B}(t) - k_{MC-B} \cdot N_{MC}(t) - \frac{\Delta N_{MC}(t,D)}{\Delta t} \tag{1e}
\]

\[
\frac{dN_{SC}(t)}{dt} = k_{SN-SC} \cdot N_{SN}(t) + k_{B-SC} \cdot N_{B}(t) - k_{SC-B} \cdot N_{SC}(t) - \frac{\Delta N_{SC}(t,D)}{\Delta t} \tag{1f}
\]

\[
\frac{dN_{LC}(t)}{dt} = k_{LN-LC} \cdot N_{LN}(t) + k_{B-LC} \cdot N_{B}(t) + k_{TC-LC} \cdot N_{TC}(t) - k_{LC-B} \cdot N_{LC}(t) - \frac{\Delta N_{LC}(t,D)}{\Delta t} \tag{1g}
\]

\[
\frac{dN_{TC}(t)}{dt} = k_{B-TC} \cdot N_{B}(t) - (k_{TC-LC} - k_{TC-TN}) \cdot N_{TC}(t) - \frac{\Delta N_{TC}(t,D)}{\Delta t} \tag{1h}
\]

\[
\frac{dN_{B}(t)}{dt} = k_{MC-B} \cdot N_{MC}(t) + k_{SC-B} \cdot N_{SC}(t) + k_{LC-B} \cdot N_{LC}(t) -
\]

\[
(k_{B-MC} + k_{B-SC} + k_{B-LC} + k_{B-TC}) \cdot N_{B}(t) - \frac{\Delta N_{B}(t,D)}{\Delta t} \tag{1i}
\]
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

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

- For circulating lymphocytes in non-blood compartment

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

- For lymphocytes in the circulating blood

\[
\Delta N_{B_i}(t + \Delta t, d_i) = N_B(t) \cdot v_i \cdot (1 - e^{-\alpha \cdot d_i}) \cdot \Delta t \cdot k_t \cdot e^{-k_t \cdot t}
\]

\[
\Delta N_B(t + \Delta t, d) = \sum_{i=1}^{6} \Delta N_{B_i}(t + \Delta t, d_i)
\]
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
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 ($\alpha$) = 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.