Modeling of Rational Combinations Between Immunotherapeutic Approaches and Radiotherapy

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RADIATION ONCOLOGY

AAPM 2018 – Nashville

Rough Outline

- Introduction / Motivation
- Important Aspects – Seminal Papers
  - Fractionation
  - Sequencing
- Immuno-RT modeling approaches
- Clinical data informing modeling
  - PET/SPECT
  - MRI
- Conclusion & Discussion

very short history of immuno + RT

- anecdotal reports have demonstrated that immune therapy with ipilimumab (human anti-CTLA4 antibody) followed by radiation can lead to extensive tumor regression in melanoma patients (~2011/12)
- Patients treated with radiation following immune therapy, in the 'maintenance phase', showed a significant survival advantage over those treated with radiation during the 'induction phase' (Barker et al. 2013)
- Exact sequencing and fractionation still unclear
- Although checkpoint inhibition is a clear breakthrough in the treatment of late stage cancer, durable responses rare (except for Melanoma)

Ipilimumab and RT in stage IV melanoma	
NCT02406183	Four 3-wk cycles of ipilimumab, SBRT (varying dose or fractionation) on days 39+43 (wk 6)
NCT01565837	
NCT02107755	
NCT01970527	Four 3-wk cycles of ipilimumab, SBRT (3 Fx/24-36 Gy) on days 1-13
NCT02659540	Four 3-wk cycles of ipilimumab, 2 RT regimens after first cycle: palliative (30 Gy in 10 Fx) or hypofractionated (27 Gy in 3 Fx)

Introduction

- Optimization & modeling play a large role in radiotherapy: delivery, fractionation, target dose, OAR tradeoffs
- Immunotherapy modeling is a comparatively recent approach
- *Aim of this talk*: to show that RT combined with immunotherapy warrants different approaches and introduce Immuno+RT modeling techniques
- Chemo-radiation to some extent been "heuristically" optimized

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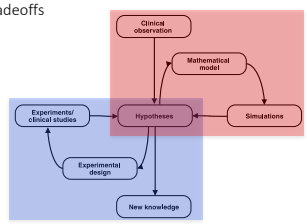

[1] Gallasch et al. 2013, Journal of Clinical Bioinformatics 2:23

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Fractionation – Dewan et al. 2009

- Hypothesis: type of dose fractionation regimen determines the ability of radiotherapy to synergize with anti–CTLA-4 antibody

Fractionated but Not Single-Dose Radiotherapy Induces an Immune-Mediated Abscopal Effect when Combined with Anti-CTLA-4 Antibody

M. Zahidunnabi Dewan,[1] Ashley E. Galloway,[1] Noriko Kawashima,[1] J. Kelth Dewyngaert,[1] James S. Babb,[2] Silvia C. Formenti,[3] and Sandra Demaria[1]

- Radiation induces an immunogenic tumor cell death and
  - alters tumor microenvironment; enhance recruitment of antitumor T cells
  - can enhance both the priming and the effector phase of the antitumor immune response
- shown that before: local RT induces a CD8 T-cell–mediated immune response inhibiting lung micromets if combined with anti-CTLA-4
- results were actually determining the dosing and fractionation of the first clinical trials testing immunotherapy + RT

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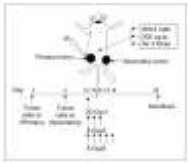
- mouse models
  - TSA breast cancer
  - MCA38 colon cancer
- in the right flank on day 0 (primary tumor) and in the left flank on day 2 (secondary tumor)
- Radiotherapy: 20Gy single dose, 3x8Gy, 5x6Gy



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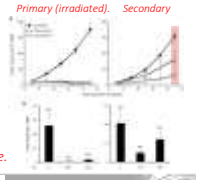
- growth of the secondary tumors was significantly inhibited ($p < 0.01$) only in mice treated with fractionated but not single-dose RT in combination with 9H10
  - regimen of 3x8Gy superior to 5x6Gy in the induction of the abscopal effect and of tumor-specific T cells

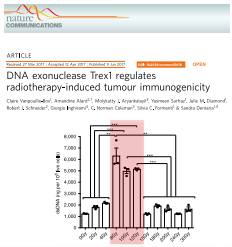
→ suggests a specific therapeutic window for the optimal use of fractionated radiotherapy in combination with CTLA-4 blockade

However, the degree to which RT by itself achieved local tumor control did not predict its ability to synergize with CTLA-4 blockade.



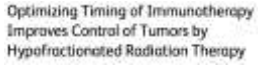
Fractionation – Vanpouille-Box et al. 2017

- Mechanism behind that thought to be connected to cytosolic DNA accumulation
- Cytosolic DNA stimulates secretion of interferon-b
  - → recruitment and activation of dendritic cells
  - → essential for priming of CD8+ T-cells
- DNA exonuclease Trex1 is induced by radiation doses above 12–18Gy
  - → degrades DNA that accumulates in the cytosol upon radiation
  - → attenuates their immunogenicity



Sequencing – Young et al. 2016

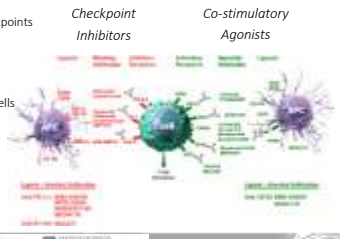
Hypothesis: depending on the mechanism of action of immunotherapy, the optimal timing of radiation and immunotherapy will be different



- little data exist regarding the ideal timing of immunotherapy combined with radiation
- test the optimal timing of two distinct immunotherapy approaches
  - checkpoint inhibitor (anti-CTLA-4)
  - co-stimulatory agonist (anti-OX40)

Checkpoint Inhibitors *vs* Co-Stimulatory Agonists

- Checkpoint inhibitors
  - downregulate T cell inhibition checkpoints
  - CTLA4 inhibitors (Ipilimumab)
  - PD1/PD-L1 inhibitors (Nivolumab)
- Co-stimulatory agonist:
  - promote division and survival of T cells
  - augmenting the clonal expansion of effector and memory populations
  - anti-OX40
  - anti-CD40



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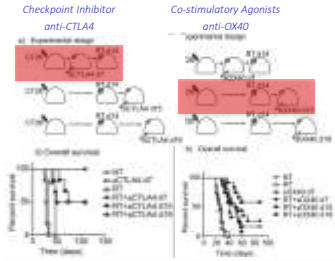

- 20Gy radiation was delivered to the tumor only, on day 14
- treated mice with anti-CTLA4 / OX40 antibody on either day 7, day 15, or day 19
- optimal timing of anti-CTLA4 is *before* radiation therapy
- optimal timing of anti-OX40 is *shortly after* radiation therapy

→ *Timing of immunotherapy in combination with RT significantly affects outcome and that the ideal timing of specific immunotherapeutic agents depends on their mechanisms of action*

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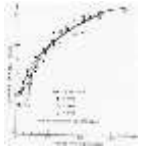
Immuno – RT modeling

- exponential growth is bad approximation over long time periods
- more realistic growth models exhibit decreasing growth rate with increasing tumor size
- most popular: Gompertz, Logistic

$$\frac{dV(t)}{dt} = r(t)V(t) \qquad \frac{dr(t)}{dt} = -r \times r(t)$$ *Gompertz*

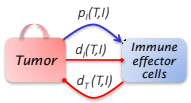


Laird 1964

Immuno – RT modeling

$$\frac{dT}{dt} = r(t) \times T$$

Immuno – RT modeling



$$\frac{dT}{dt} = r(t) \times T - d_T(T,I)$$

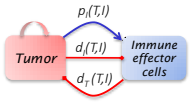
$$\frac{dI}{dt} = p_I(T,I) - d_I(T,I) - a_I(I) + j(t)$$

production/death

apoptosis

treatment

Immuno – RT modeling



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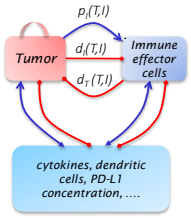
Michaelis-Menten dynamics:

$$\frac{dI}{dt} = \frac{c_{\max} \times T}{s + T} I$$

Immuno – RT modeling



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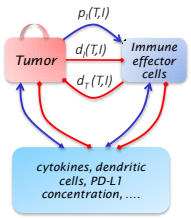
Immuno – RT modeling



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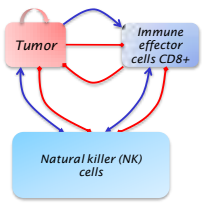
- These very simple models can reproduce the basic behaviours of the tumor-immune interaction: elimination - equilibrium - escape

Example - dePillis *et al.* 2005-09



- Model includes
  - Innate immunity: NK cells
  - Adaptive immunity: CD8+ T cells
- Purpose: to study the relative importance of these 2 populations for long-term tumor control

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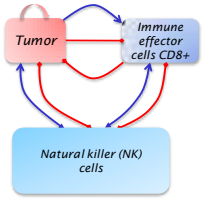

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Tumor $\frac{dT}{dt} = aT(1-bT) - cNT - D$

NK

CD8+

dePillis Cancer Res 2005; 65: (17)

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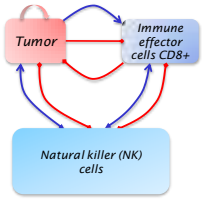

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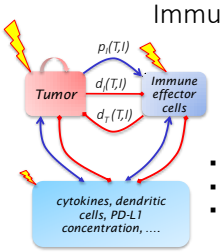
- Outcome most sensitive to CD8+ tumor lysis term -> can be measured in assay

dePillis Cancer Res 2005; 65: (17)

Immuno – RT modeling



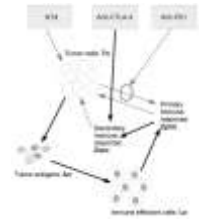
$$\frac{dT}{dt} = r(t)T - d_T(T,I) - R_T(T)$$

$$\frac{dI}{dt} = p_I(T,I) - d_I(T,I) - a_I(I) - R_I(I)$$

Radiation effect

- Differential between populations
- Not coupled
- Indirect effects:
  - Model-implicit ones
  - Model-explicit ones

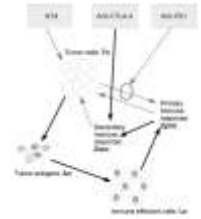
Example – Serre *et al.* 2016



- Cell populations includes
  - Tumor
  - Immune effector cells
  - Tumor Antigens
- 2 pathways in which immune effector cells affect Tumor
  - To model 2 drugs: anti-CTLA-4 and anti-PD-1

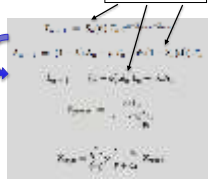
Serre *et al.* Cancer Res 2016; 76(17)

Example – Serre *et al.* 2016



Explicitly modeled indirect interaction: tumor – lymphocytes interaction only over A_n and immune response

Radiation effect



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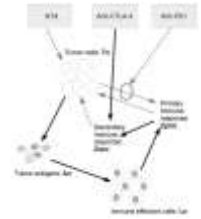

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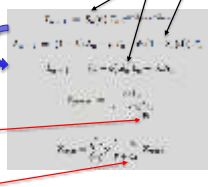
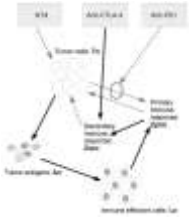


Anti-PD1: affects downregulation of immune response by tumor

Anti-CTLA-4: promotes proliferation of T cells for memory response

Serre *et al.* Cancer Res 2016; 76(17)

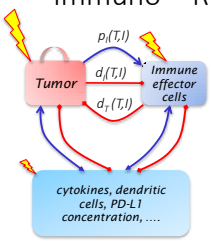
Example – Serre *et al.* 2016

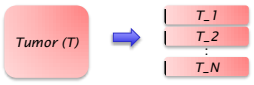


- proposed model is able to describe correctly
  - the immunogenicity of a tumor as a function of its size
  - Murine model results for irradiation combined with CTLA-4 and PD-1 inhibitors
- Model tailored to these two drugs
  - No fractionation dynamics

Serre *et al.* Cancer Res 2016; 76(17)

Immuno – RT modeling: local models



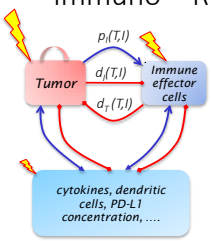


- Main motivation: target selection for RT in stage IV disease
- Hypothesis: choice of site for localized therapy determines potential for systemic response

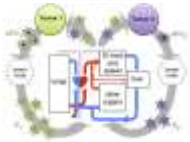
Polesczuk *et al.* Cancer Res 2016; 76(5)

Walker *et al.* Scientific Reports (2018) 8:9474

Immuno – RT modeling: local models



- Need additional information: T cell trafficking between sites



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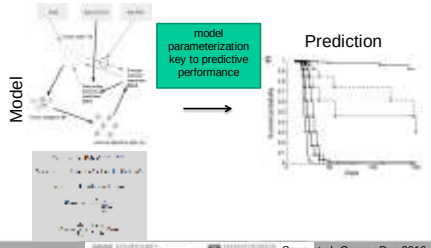
From Model to Prediction – Model Parameterization



Serre et al. *Cancer Res 2016*

Achilles heel – model parameters

- Table describing models parameters of a tumor-immune model (dePillis et al. 2005)
- Most models based on experimental murine model data

Parameters	Units	Estimated value	Description	Source
a	day^{-1}	5.14×10^{-1}	Tumor growth rate	(6)
b	$cell^{-1}$	1.02×10^{-9}	1/k in tumor carrying capacity	(6)
$r(m)$	$cell^{-1} \cdot day^{-1}$	3.23×10^{-7}	Fractional (non)-ligand-transduced tumor cell kill by NK cells	(6)
$r(t)$		3.00×10^{-6}		
$d(m)$	day^{-1}	1.41	Saturation level of fractional tumor cell kill by CD8$^+$ T cells, challenged with (non)-ligand-transduced cells.	(6)
$d(t)$		5.00		
$d(n)$		3.31		
$d(l)$		1.17		
$\lambda(m)$	None	5.80×10^{-1}	Exponent of fractional tumor cell kill by CD8$^+$ T cells, on, nl, ln, ll primed with (non)-ligand-transduced cells, challenged with (non)-ligand-transduced cells.	(6)
$\lambda(nn)$		4.60×10^{-1}		
$\lambda(ln)$		9.00×10^{-1}		
$\lambda(ll)$		7.20×10^{-1}		
$s(m)$	None	2.73	Steepness coefficient of the Tumor-(CD8$^+$ T cell) competition term, on, nl, ln, ll primed with (non) ligand-transduced cells, challenged with (non)-ligand-transduced cells (smaller s=steeper curve)	(6)
$s(nl)$		1.61		
$s(ln)$		5.07		
$s(l)$		4.00×10^{-1}		
e	$cells \cdot day^{-1}$	1.20×10^{6}	Constant source of NK cells.	(10)
f	day^{-1}	4.12×10^{-2}	Death rate of NK cells.	(10)
$g(n)$	day^{-1}	2.5×10^{-7}	Maximum NK cell recruitment rate by (non) ligand-transduced tumor cells. $g(n) = 2 \times 10^{-7}$	(10, 6)
k	$cell^{1}$	2.02×10^{7}	Steepness coefficient of the NK cell recruitment curve	(10)
p	$cell^{-1} \cdot day^{-1}$	1.0×10^{-7}	NK cell inactivation rate by tumor cells	(6)
m	day^{-1}	3.0×10^{-1}	Death rate of CD8$^+$ T cells	(27)
$j(nn)$	day^{-1}	3.75×10^{-2}	Maximum CD8$^+$ T cell recruitment rate, nn, nl, ln, ll primed with (non)-ligand-transduced cells, challenged with (non)-ligand-transduced cells. $j(nn) = 1.25 \times 10^{-1}$	(10, 6)
$j(nl)$		3.75×10^{-2}		
$j(ln)$		$3(nn) = 1.25 \times 10^{-1}$		
$j(ll)$		$3(nn) = 3.6 \times 10^{-2}$		
k	$cell^{1}$	2.02×10^{7}	Steepness coefficient of the CD8$^+$ T cell recruitment curve	(10, 6)
q	$cell^{-1} \cdot day^{-1}$	5.42×10^{-9}	CD8$^+$ T cell inactivation rate by tumor cells	(10)
r	$cell^{-1} \cdot day^{-1}$	1.1×10^{-7}	Rate at which tumor specific CD8$^+$ T cells are stimulated to be produced as a result of tumor cells killed by NK cells	(27, 29)

dePillis Cancer Res 2005; 65: (17)

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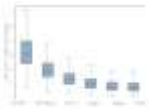
Correlation Lymphocyte Count – Survival

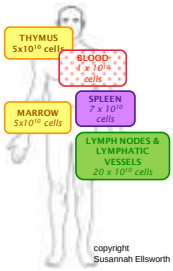
- independent of indication lymphocyte counts during chemo-radiation all look similar



Davuluru et al. *IJROBP 2017*

Correlation Lymphocyte Count – Survival

- independent of indication lymphocyte counts during chemo-radiation all look similar
- only provide a snapshot of the lymphatic system
  - Circulating lymphocytes only present ~2-5% of the total population



copyright Susannah Ellsworth

Correlation Lymphocyte Count – Survival

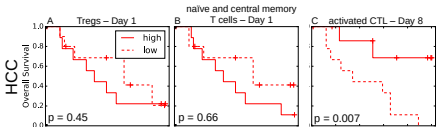
	Site	N	Tx	measure & timepoints	HR for OS	
Mendez et al. 2017	GBM (elderly >=65)	72	radiation +TMZ	TLC, monthly after intiation	**2.76** [1.3-5.86]	
Liu et al. 2017	nasopharynx	413	cCRT (gem)	ALC, weekly during, directly post, 3m post	**1.76** [1.12-2.78]	
Chadha et al. 2017	pancreas	177	induction (gem) + cCRT	ALC, 2-10 weeks after	**1.66** [1.13-2.43]	spleen DVH study
Tang et al 2014	NSCLC	711	RT+- chemo	ALC, "continuously" throughout irradiation	**1.96 ***	correl low-dose bath with lymph
Cho et al 2016	cervix	124	cCRT (weekly cis)	ALC, weekly during	**3.28** [1.27-8.48]	
Cho et al 2016b	LS-SCLC	73	s/cCRT (EP)	ALC, weekly during	**2.67** [1.06–6.75]	
Davuluri et al 2017	esophagus	504	CRT (def or neoadj)	ALC, weekly during	**1.35**	proton vs photon
Grassberger et al 2017*	liver	44	RT +- induction	Lymphocyte panel, weekly during	-	proton only

Lymphocyte Sub-Populations

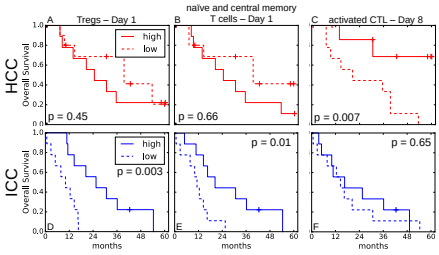
- Evaluated 4 lymphocyte sub-populations during RT in liver cancer patients, including hepatocellular carcinoma (HCC) and intra-hepatic cholangiocarcinoma (ICC) patients :
  - CD4+CD25+
regulatory T cells (Tregs)
  - CD4+CD127+
naïve and central memory T cells
  - CD3+CD8+CD25+
activated cytotoxic T lymphocytes (CTLs)
  - CD3–CD56+
natural killer (NK) cells

Grassberger et al. *IJROBP 2018*

Differential Association with Survival



Differential Association with Survival



Differential Association with Survival

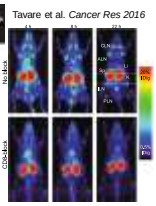
- differential association with survival
  - ICC: OS was significantly correlated with greater Treg (p=0.003) and naïve and central memory T cell (p=0.01) fractions at baseline
  - HCC: fraction of activated CTLs mid-treatment (at day 8) was significantly associated with OS (p=0.007).
- Importance of investigating lymphocyte sub-populations
  - clearer "signal"
  - differential immunosuppression in different indications

Imaging the Immune Response

- PET/SPECT
  - antibody-labeling


An Effective Immuno-PET Imaging Method to Monitor CD8-Dependent Responses to Immunotherapy

Tavare et al. *Cancer Res 2016*

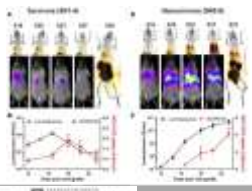


- use ^{89}Zr-desferrioxamine–labeled anti-CD8 for non-invasive immuno-PET tracking of endogenous CD8+

Imaging the Immune Response

- PET/SPECT
  - antibody-labeling
  - cell-labeling

Vedvyas et al. JCI Insight 2016



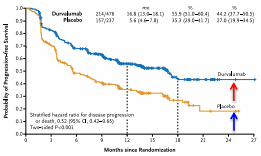
- used PET to quantitatively and longitudinally visualize whole-body CAR-T cell distribution
- observed kinetics after infusion into tumor-bearing mice at different time points → bi-phasic T cell expansion and contraction

Imaging the Immune Response

- MRI: super-paramagnetic iron oxide nanoparticles (SPIONs)
  - generally phagocytosed by monocytes and macrophages, allowing for image contrast in inflammatory conditions such as infections
  - ex vivo labeling and in vivo tracking of specific cell populations, such as dendritic cells or other leukocytes
  - MRI-based techniques have the advantage of excellent spatial resolution, two major short-comings
    1. sensitivity of MRI is somewhat low, preventing the detection of responses which are not densely populated by the cells of interest.
    2. direct quantification can be difficult in MRI

The Case for Immunotherapy-RT Modeling

- Immune checkpoint inhibitors → stage III NSCLC
  - PACIFIC trial: Durvalumab (PD-L1) after chemo-radiation in stage III NSCLC



adjuvant Immunotherapy

Chemo-radiation to 60-66Gy in 2Gy/fx

  - (concurrent) chemo-radiation is optimized for maximum cell kill, not maximum immune response
  - optimal treatment regimen is different (as shown previously)

Conclusion & Takeaways

- Preclinical experiments showing importance of fractionation & sequencing
- Modeling Immuno-RT
  - ODE based systems
  - Tailored to immune-drug interaction, not radiotherapy
  - Fractionation/RT dose not explored yet

Conclusion & Takeaways

- Preclinical experiments showing importance of fractionation & sequencing
- Modeling Immuno-RT
  - ODE based systems
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  - Fractionation/RT dose not explored yet
- Global *vs* Local models
  - Tumor seen as one compartment *vs* explicit treatment of different metastatic sites
  - Informing different questions in stage III/IV
  - emerging question in stage III disease:

Is the purpose of the (chemo-)RT regimen to
maximize cell kill ?
OR
maximize / modulate the immune response ?

Conclusion & Takeaways

- Preclinical experiments showing importance of fractionation & sequencing
- Modeling Immuno-RT
  - ODE based systems
  - Tailored to immune-drug interaction, not radiotherapy
  - Fractionation/RT dose not explored yet
- Global *vs* Local models
- trade-off in general dose level / intensity of chemo-RT
  - radiation eliminates tumor cells -> decreases the tumorinduced immunosuppression
  - Highdose radiation is associated with increased antigen expression and induction of immunogenic cell death
  - High-dose radiation is also associated with depletion of lymphocytes, dampening immune responses

Conclusion & Takeaways

- Preclinical experiments showing importance of fractionation & sequencing
- Modeling Immuno-RT
  - ODE based systems
  - Tailored to immune-drug interaction, not radiotherapy
  - Fractionation/RT dose not explored yet
- Global *vs* Local models
- trade-off in general dose level / intensity of chemo-RT
- Immune Surveillance techniques
  - Lymphocyte counts - Global
    - Emerging interest in lymphocyte subpopulations
  - Imaging (PET/SPECT/MRI) - Local
    - Dynamic information

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