Modeling of Therapy Response in Oncology

Clemens Grassberger

Drug - Radiation

Treatment Design Lab

HARVARD MEDICAL SCHOOL

MASSACHUSETTS GENERAL HOSPITAL

RADIATION ONCOLOGY

AAPM 2019 – San Antonio, TX

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#AAPM2019
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Outline

- Introduction / Motivation
- Dynamic models
  - chemo-radiation as an example
- Modeling molecularly targeted agents
  - deriving population dynamics from macroscopic tumor volume trajectories
- Modeling Immunotherapy (+RT)
- Conclusion & Discussion

Introduction

- Mathematical modeling & optimization plays a large role in radiotherapy
  - Delivery – treatment planning
  - Fractionation – NTCP/TCP trade-offs
  - Target dose – BED
  - MCO – OAR tradeoffs
- Emerging also for design of drug regimen (#mathonco)

Aim: introduce a cross section of mechanistic mathematical models for trial design & patient-specific treatment adaptation

Mechanistic Mathematical Modeling & its place in the ecosystem

Clinical Observations
on different scales:
- Outcome
- Imaging
- Omic / biomarker

Improved treatment
- Treatment scheduling
- Combination treatments
- New compounds
- Drug dynamics

Figure idea
Ryan O Schenk
@research_junkie

Mechanistic Mathematical Modeling & its place in the ecosystem

Clinical Observations
on different scales:
- Outcome
- Imaging
- Omic / biomarker

Statistical Modeling
- What and when?
- Observed relationship

Improved treatment
- Treatment scheduling
- Combination treatments
- New compounds
- Drug dynamics

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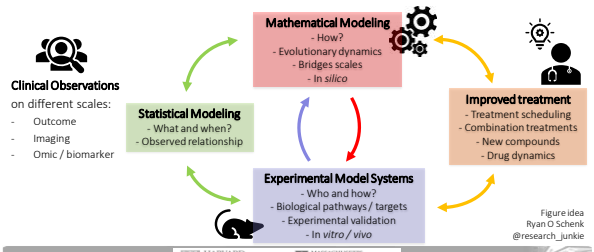
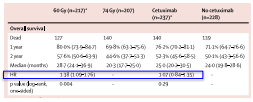
Mechanistic Mathematical Modeling & its place in the ecosystem



Modeling interaction of chemotherapy & radiation

- Simplest way to quantify the effect: Hazard Ratio



Bradley et al. (2015) Lancet

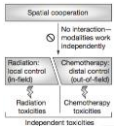
Modeling interaction of chemotherapy & radiation

- Simplest way to quantify the effect: Hazard Ratio
- Include them in TCP models
  - Independent action

Chemo-only survival Radiation-only survival

$$OS = CS + RS\,(1 - CS)$$

chemo equals a dose of X GyE



Seiwert et al. (2007), Nat Clin Prac Onc

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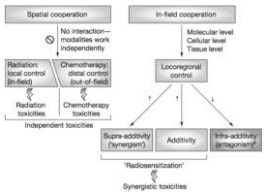
  - Radiosensitization: TCP = f(BED)

$$BED = f_c D \cdot \left(1 + \frac{f_c * d}{\alpha/\beta}\right) - \frac{\ln 2}{\alpha} \cdot \frac{T}{T_d}$$

Radiosensitization factor: f_c



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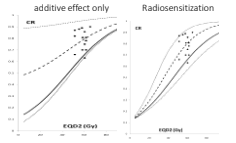


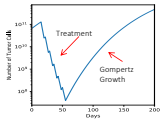
Plataniotis et al. (2014) IJROBP

Dynamic Models of Therapy

- formulations often based on ordinary differential equations
  - Tumor growth: Gompertz
  - Radiation cell kill - Linear-Quadratic: $SF = e^{-(aD+bD^2)}$
  - Chemo cell kill - Log cell kill: $SF = e^{-(aD(t))}$

$$\frac{dN}{dt} = r\,N(t)\log\left(\frac{K}{N(t)}\right) - b_c C(t) N(t) - \left(aD + bD^2\right) N(t)$$

Growth (Gompertz) | Chemotherapy (LOG cell kill) | Radiation (Linear Quadratic)

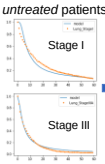


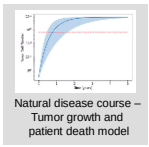
Modeling Multi-Modality Therapy for NSCLC

$$\frac{dN}{dt} = rN(t)\log\left(\frac{K}{N(t)}\right) - b_c C(t)N(t) - \left(aD + bD^2\right)N(t)$$

Geng et al. *Scientific Reports* 2017

Survival of *untreated* patients

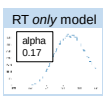




Natural disease course – Tumor growth and patient death model

Modeling Multi-Modality Therapy for NSCLC

RT *only* model



Radiosensitivity distribution

RTOG 8808 radiation-only trials

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Geng et al. *Scientific Reports* 2017

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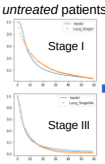

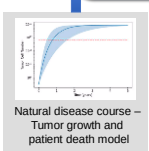

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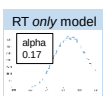

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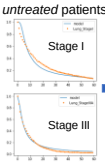
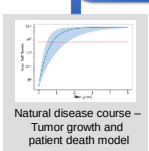
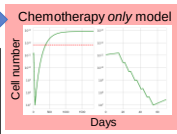


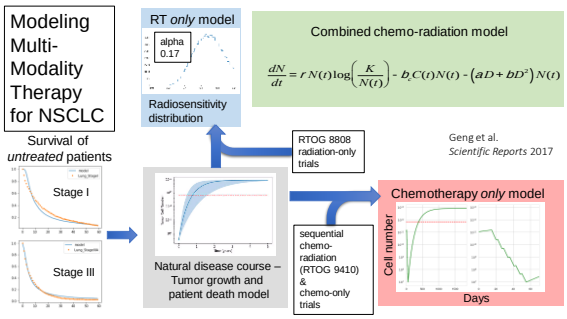


Natural disease course – Tumor growth and patient death model

sequential chemo-radiation (RTOG 9410) & chemo-only trials

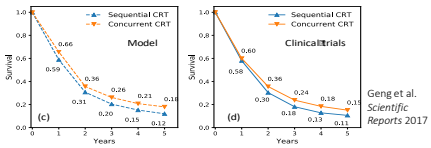
Chemotherapy *only* model





Dynamic Models of Therapy

- Explicitly time-dependent
  - ability to explore different sequencing options
  - Uses underlying clinical data for fitting more effectively



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Dynamic Models of Therapy

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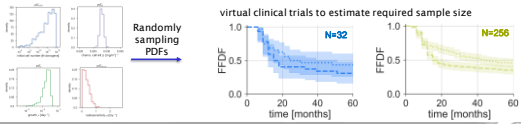
- Based on distributions of parameters describing a heterogeneous patient population
  - Pro: Monte Carlo sampling techniques for more accurate sample size calculations



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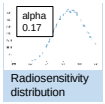

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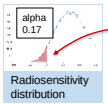

Radiosensitivity Index (RSI)

A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study

Dynamic Models of Therapy

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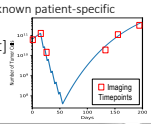
- Explicit modeling of tumor dynamics over time [dN(t)/dt]

enables connection to individual tumor trajectories via serial imaging studies



Dynamic Models of Therapy

- provides a framework to include other modalities, such as targeted agents

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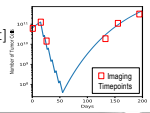

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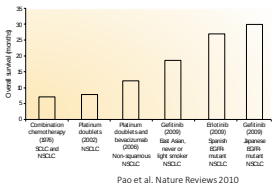
- Introduction / Motivation
- Dynamic models
  - chemo-radiation as an example
- Modeling molecularly targeted agents
  - deriving population dynamics from macroscopic tumor volume trajectories
- Modeling Immunotherapy (+RT)
- Conclusion & Discussion

Targeted Therapy

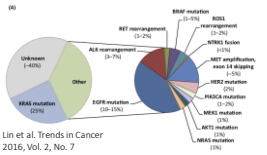
- Very successful in Non-Small Cell Lung Cancer (NSLC)



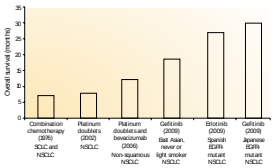
Pao et al. Nature Reviews 2010

Targeted Therapy

- Very successful in Non-Small Cell Lung Cancer (NSLC)
- Main oncogenic driver mutations for which FDA-approved inhibitors exist: EGFR & ROS/ALK



Lin et al. Trends in Cancer 2016, Vol. 2, No. 7



Pao et al. Nature Reviews 2010

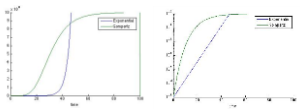
- better toxicity profiles

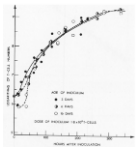
→ different mode of administration to chemo; not IV in cycles, but daily oral uptake

Targeted Agent Effect Models

- Similar to chemo, but need something additional → resistant sub-populations
- Modeling more sensitive to exact growth models
  - 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

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

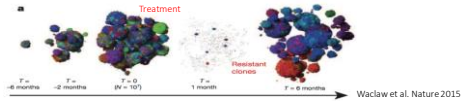




Laird 1964

Targeted Agent Effect Models

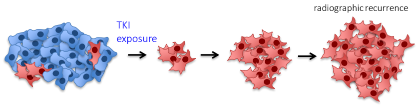
- Similar to chemo, but need something additional → resistant sub-populations
- Modeling more sensitive to exact growth models
- Resistance development
  - Mathematical formulation based on work in bacteriology (Luria & Delbrueck)
  - Used stochastic processes with a differentiation hierarchy to represent sensitive & resistant cells



Waclaw et al. Nature 2015

Modeling Resistance

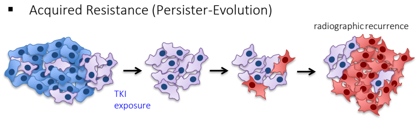
- Pre-Existing Resistance



TKI-sensitive population N_S	$\frac{dN_S(t)}{dt} =$	$l_S \times N_S(t)\log\frac{K(t)}{N_S(t)}$	growth in absence of drug
		$-\,b \times l_S \times N_S(t)\log\frac{K(t)}{N_S(t)}$	cell loss in presence of drug
TKI-resistant population N_R	$\frac{dN_R(t)}{dt} =$	$l_R \times N_R(t)\log\frac{K(t)}{N_R(t)}$	growth independent of presence of drug

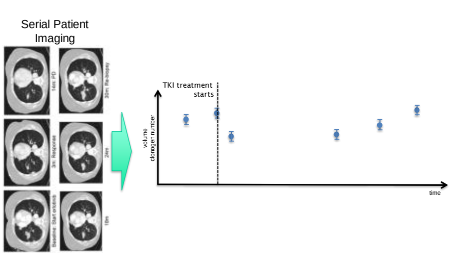
Modeling Resistance

- Pre-Existing Resistance
- Acquired Resistance (Persister-Evolution)



persister population N_P	$\frac{dN_P(t)}{dt} =$	$-t(P \rightarrow R) \cdot N_P(t)$	transition to resistant cells
TKI-resistant population N_R	$\frac{dN_R(t)}{dt} =$	$l_R \times N_R(t)\log\frac{K(t)}{N_R(t)}$	growth independent of presence of drug
		$+t(P \rightarrow R) \cdot N_P(t)$	transition from persister cells

Modeling Resistance – Tumor Growth Trajectories



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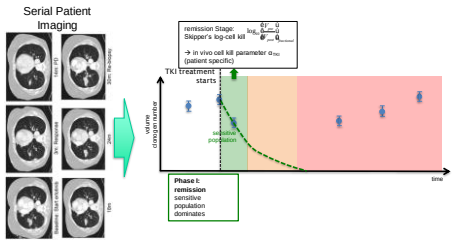

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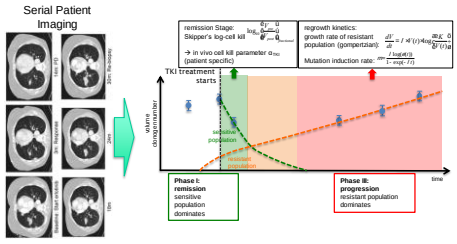

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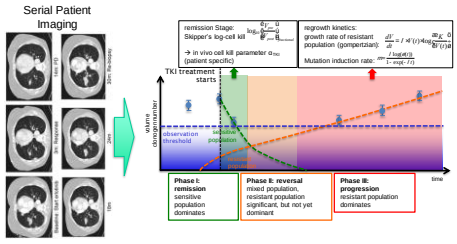

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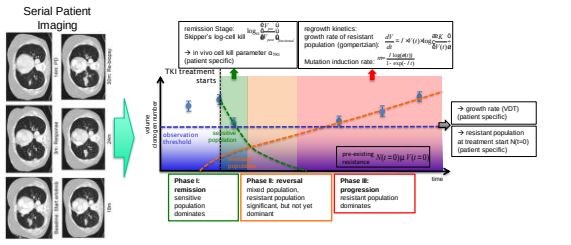

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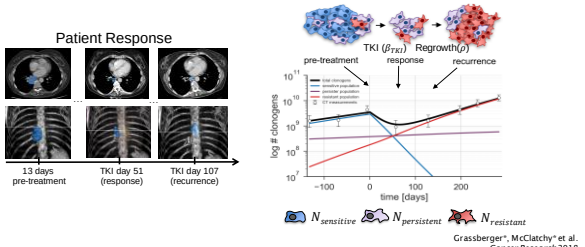

Grassberger*, McClatchy* et al. *Cancer Research* 2018

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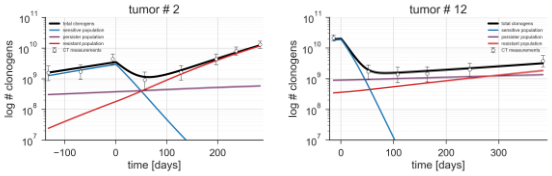
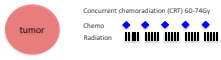


- Based on macroscopic tumor volume trajectories, we can estimate the dynamics of persister/resistant cells during treatment with targeted agents

Rationale for Modeling

- Targeted agents currently only used in a stage IV setting
- Targetable mutations also exist in stage III disease



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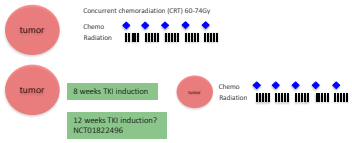
→ NCT01553942 – the ASCENT trial



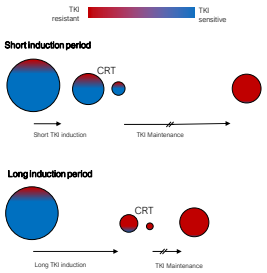
Rationale for Modeling

- Scenario I: TKI induction– TKI serves as clonogen reduction to support CRT

Rationale for Modeling

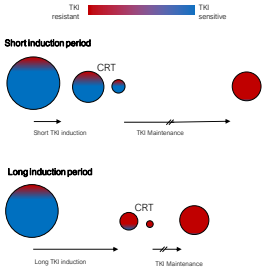
- Scenario I: TKI induction– TKI serves as clonogen reduction to support CRT

- Scenario II: TKI Maintenance therapy – chemo-radiation should be employed to minimize resistance development



Bo McClatchy - Modeling Local Versus Distant Tumor Recurrence in Non-Small Cell Lung Cancer Patients Receiving Combined Chemoradiotherapy and Molecularly Targeted Drugs

Session: Image Analysis for Response Assessment
Time: Wed 7/17 8:30am
Room: 225 BCD



Open Questions

- Can we use only targeted agents + RT (without chemotherapy)?
  - Best combination / sequencing?
- Does this differ when treating oligometastatic disease (stage IV) with RT?
- …

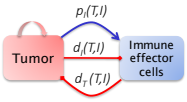
Outline

- Introduction / Motivation
- Dynamic models
  - chemo-radiation as an example
- Modeling molecularly targeted agents
  - deriving population dynamics from macroscopic tumor volume trajectories
- Modeling Immunotherapy (+RT)
- Conclusion & Discussion

Immuno – RT modeling

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

Immuno – RT modeling



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

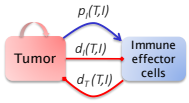
$$\frac{dI}{dt} = p_I(T,I) - d_I(T,I) - a_I(I) + j(t)$$

production/death

apoptosis

treatment

Immuno – RT modeling



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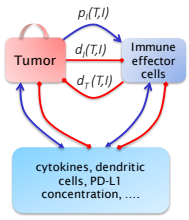
Michaelis-Menten dynamics:

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

Immuno – RT modeling



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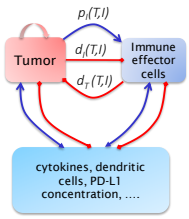

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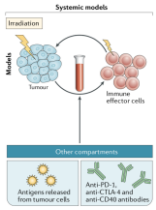
$$\frac{dI}{dt} = p_I(T,I) - d_I(T,I) - a_I(I) + j(t)$$

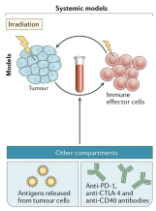
- These very simple models can reproduce the basic behaviours of the tumor-immune interaction: elimination - equilibrium - escape

Systemic vs Regional-Interacting Models



Grassberger et al. *Nat Rev Clin Onc* 2018

Systemic vs Regional-Interacting Models



Wonmo Sung

"Modeling of Tumor and Immune Cell Interactions in Hepatocellular Carcinoma Patients treated with RT"

Grassberger et al. *Nat Rev Clin Onc* 2018

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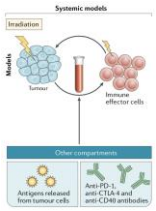
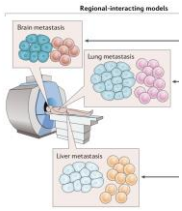
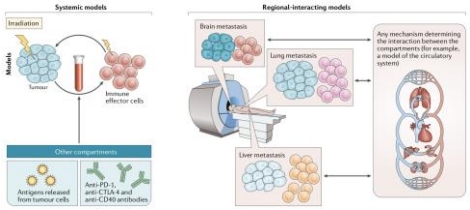




Multiple tumor and local lymphocyte compartments

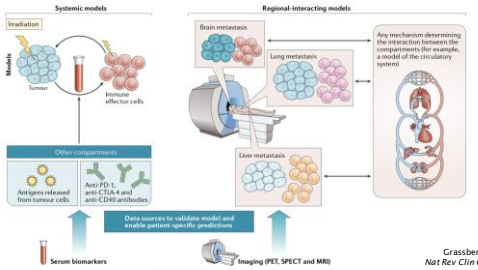
Grassberger et al. *Nat Rev Clin Onc* 2018

Systemic vs Regional-Interacting Models



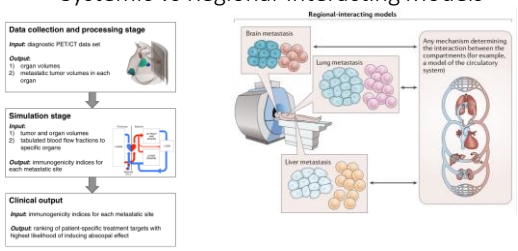
Grassberger et al.
Nat Rev Clin Onc 2018

Systemic vs Regional-Interacting Models



Grassberger et al.
Nat Rev Clin Onc 2018

Systemic vs Regional-Interacting Models

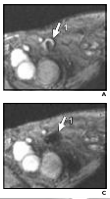


Rachel Walker et al. 2017
Converg Sci Phys Oncol

Grassberger et al.
Nat Rev Clin Onc 2018

Imaging the Immune Response

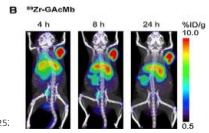
- MRI
  - Several magnetic contrast agents for visualizing the immune response
    - superparamagnetic iron oxide nanoparticles (SPION)
  - 2 major shortcomings:
    - Low sensitivity - if population of interest is low density …
    - direct quantification of signal (e.g. molar concentration of contrast agents) can be difficult



Bulte et al. NMMI 2009

Imaging the Immune Response

- MRI
- SPECT /PET
  - preclinical studies have reported successful imaging of T and B cell populations using radiotracer-labeled anti- T and anti-B cell antibodies, or antibody fragments



Zettlitz et al. 2017 Clin Cancer Res 23, 7242–725.

Imaging the Immune Response

- MRI
- SPECT /PET

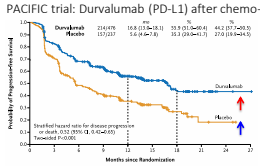
Assessing the interactions between radiotherapy and antitumour immunity

Clemens Grassberger[1]*, Susannah G. Ellsworth[2], Moses Q. Wilks[3], Florence K. Keane[1] and Jay S. Loeffler[1]

The Case for Immunotherapy-RT Modeling

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

Summary I

- Dynamic models of tumor development and therapy effect enable connection to serial imaging analyses
- Combining RT with targeted agents requires new approaches & extended models
  - Growth – realistic growth models due to longer time frames
  - Resistance – emergence of completely resistant sub-populations
- shifting aims – is the purpose of the RT regimen either to
  - maximize cell kill OR
  - minimize resistance development (to EGFR/ALK/ROS inhibitor)
- Essential for their inclusion in stage III, raises interesting question/trade-off:
  - is RT there to support the agent or the other way round?

Summary II

- Modeling Immunotherapy + RT
  - Immune response imaging techniques (MRI, SPECT, PET)
- Systemic *vs* Regional-Interacting models
  - Tumor seen as one compartment *vs* explicit treatment of different 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 ?

Acknowledgements

Drug Radiation Treatment Design Lab

Drug Radiation Treatment Design Lab
- Bo McClatchy, PhD
- Wonmo Sung, PhD
- Changran Geng PhD

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- Harald Paganetti, PhD
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- Aimee McNamara, PhD
- David Craft, PhD

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- Henning Willers MD
- Sophia Kamran MD
- Zofia Piotrowska MD
- Lecia Sequist MD

NIH NATIONAL CANCER INSTITUTE

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NCI CA059267
NCI CA241918

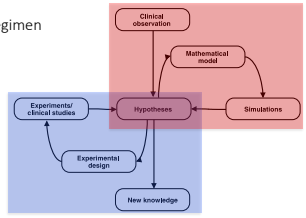
Prevalence of Concurrent Therapy → potential for Targeted Agents + RT

- Patients treated with combined chemo-radiation

Site	Incidence US 2015 number in '000 (% of total)	Percentage treated with chemotherapy and radiation	Targetable mutations
Breast	234 (14.1)	25%	HER2, mTor, CDK4/6
Lung	221 (13.3)	29%	EGFR, ALK, ROS, VEGF(R2), MET, PD-1
Colon	93(5.6)	40%**	VEGF(R2), EGFR, KIT/RAF
Bladder	74(4.5)	30%**	Possibly EGFR, FGFR3, mTOR, PIK3CA, RAS,
Non-HL	72(4.3)	12%	CD20/30, PI3K
Uterine corpus	55(3.3)	12%**	VEGF
Head and Neck	46(2.8)	30%*	EGFR, PI3K, Notch
Rectal	40(2.4)	12%	VEGF(R2), EGFR, KIT/RAF
Total	**835 (50.4)**	**26%**	

Introduction

- Optimization plays a large role in radiotherapy: delivery, fractionation, target dose, OAR tradeoffs
- Emerging role in design of drug regimen (example to follow)
- General aim: introduce *clinically applicable* models to help in trial design & patient-specific treatment adaptation



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

Overview over Clinical Studies

- Additive Effects:
  - Head and Neck: 7-12 Gy
  - Anal Cancer: 4-8 Gy
  - Cervical Cancer: 0.5-8 Gy
- radiosensitization factors: 1.2-1.35 in pancreas & bladder

Table 3. Quantified chemotherapy contributions either as chemo-equivalent radiation dose or as radiosensitization factor.

Source	Site	Effect type	Effect of chemotherapy
Plataniotis and Dale (2008)	Cervix	Independent action	Equivalent to 0.4–8 Gy in 2 Gy fractions, depending on tumor radiosensitivity
Kasibhatla *et al* (2007) and Fowler (2008)	Head and neck	Independent action	Equivalent to 8.8 $Gy_{2.0}$ or 7.6 Gy in 2 Gy fractions
Monaru *et al* (2014)	Pancreas	Sensitization only	Radiosensitization factor 1.18–1.35
Plataniotis and Dale (2014)	Bladder	Independent action *or* sensitization	Equivalent to 36.3 Gy in 2 Gy fractions *or* radiosensensitization factor of 1.3
Durante *et al* (2015)	Pancreas	Independent action	Equivalent to 94 $Gy_{5.0}$
Hartley *et al* (2010)	Head and neck	Independent action	Equivalent to 9.3 $Gy_{2.0}$ for tumor and 6.4 $Gy_{2.0}$ for mucosa
Petit *et al* (2013)	Head and neck	Independent action	Equivalent to 3–12.7 $Gy_{2.0}$, depending on chemotherapy regimen
Petit *et al* (2013)	Anal	Independent action	Equivalent to 4.1 $Gy_{2.0}$ for 5-FU and 9.1 $Gy_{2.0}$ for MMC/5-FU

Grassberger & Paganetti, PMB 2016

Overview over Clinical Studies

- Additive Effects:
  - Head and Neck: 7-12 Gy
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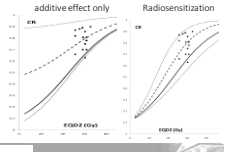
- Main Challenge: low "dimensionality" of clinical outcome data makes fitting of complex models difficult



Overview over Clinical Studies

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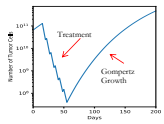
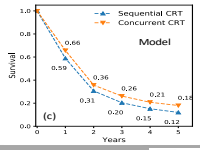
  - Cervical Cancer: 0.5-8 Gy
- radiosensitization factors: 1.2-1.35 in pancreas & bladder
- Main Challenge: low "dimensionality" of clinical outcome data makes fitting of complex models difficult
- One solution: use the whole survival curve, or even patient-level data to inform models
- dynamic models of clonogenic growth

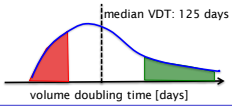


Concurrent vs Sequential CRT

- Idea: to combine radiation-only & chemo-only models → derive in-vivo radiosensitization factor
- Difference between concurrent and sequential explained by shorter treatment time

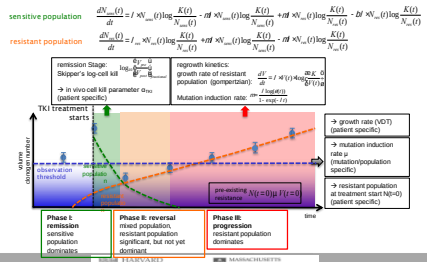
→ stratify the patients by growth rate results in variable difference between sequential and concurrent CRT



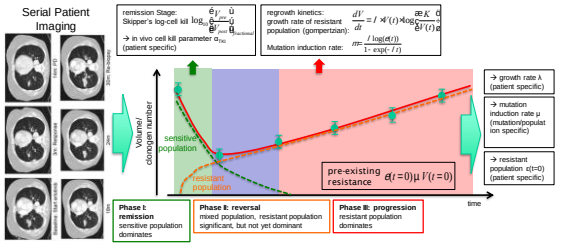


survival benefit concurrent vs sequential at 5 years	
top quartile	14.1%
bottom quartile	0.9%

dynamics of resistance

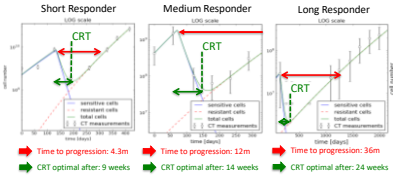


Modeling Resistance – Tumor Growth Trajectories



Rationale for Modeling

- Targeted agents currently only used in a stage IV setting
- Targetable mutations also exist in stage III disease
- Application: to find optimal induction lengths for stage III patients (patient-specific?)



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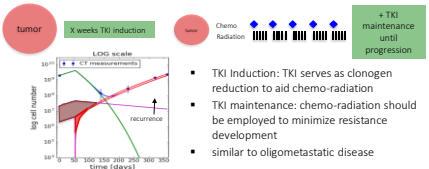
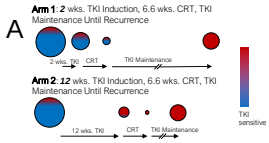
- Maintenance therapy



- TKI Induction: TKI serves as clonogen reduction to aid chemo-radiation
- TKI maintenance: chemo-radiation should be employed to minimize resistance development
- similar to oligometastatic disease



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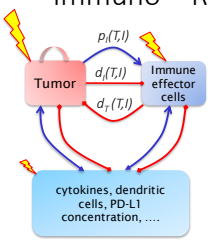
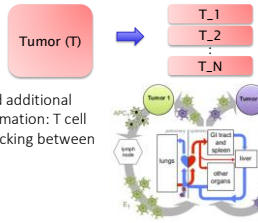
Immuno – RT modeling: local models



- Need additional information: T cell trafficking between sites



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

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

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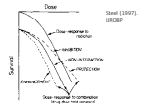
Types of Modeling Approaches

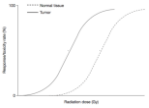
- Two "axes" on which models can be distinguished:
  - General <-> Site-Specific
  - Phenomenological <-> Mechanistic
- Models parameterized using
  - in vitro data
  - clinical patient data
- Focus on clinical applicability

→ phenomenological models based on outcome data

in vitro



clinical data



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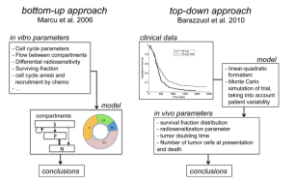
Modeling Therapy

- Two typical methods to develop a mathematic model



Which approach is advisable depends on the research question and available data at hand, but generally it is assumed that:

- top-down approaches yield parameters that are closer to the in vivo situation,
- bottom-up models allow for more extrapolation outside of current clinical experience.

Grassberger & Paganetti, PMB 2016

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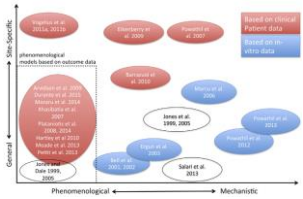

Grassberger & Paganetti, PMB 2016

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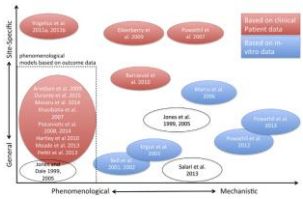

Grassberger & Paganetti, PMB 2016