Radiation Therapy Dose Response Modeling and Optimization of Fractionation Schedules with Cancer Stem Cells

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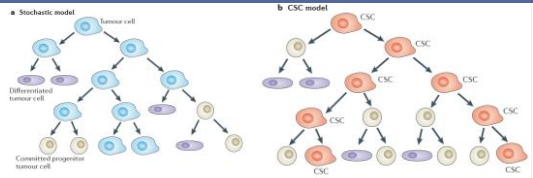
UCLA Health

Stochastic vs. Cancer Stem Cell (CSC) Models



- All cells equipotent
- Stochastically self-renew and differentiate

- A small subset of cells have higher capacity of self-renewal
- Multipotent

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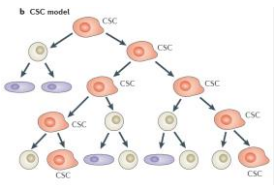
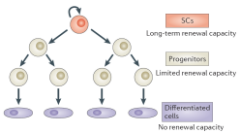
[1] Reya T et al., Nature 2001 [2] Clarke MF et al., Cancer Res 2006 [3] Baumann et al. Nat Rev Ca 2008

The Cancer Stem Cell (CSC) Hypothesis



- These cells give rise to committed progenitors with limited proliferative potential that eventually terminally differentiate



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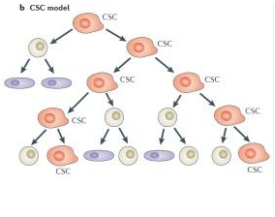
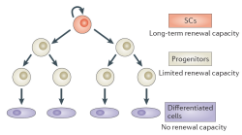


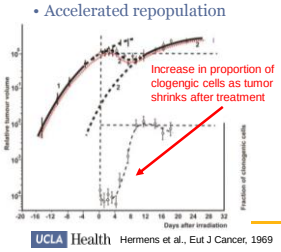
- Solid tumor is consist of:
  - Cancer stem cells (CSC)
  - Differentiated cancer cells (DCC)



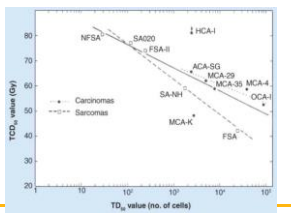
UCLA Health [1] Reya T et al., Nature 2001 [2] Clarke MF et al., Cancer Res 2006 [3] Baumann et al. Nat Rev Ca 2008 4

Historic radiobiological phenomenon supporting the existence of CSC

- Accelerated repopulation



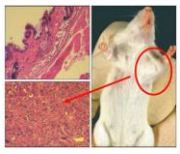
- Stem-ness and radio-resistence

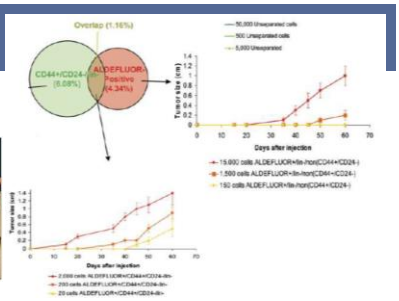


UCLA Health Hermens et al., Eut J Cancer, 1969 Hill RP et al., IJROBP. 1989 5

Breast CSC

- CD44+/CD24- or ALDH+ expression

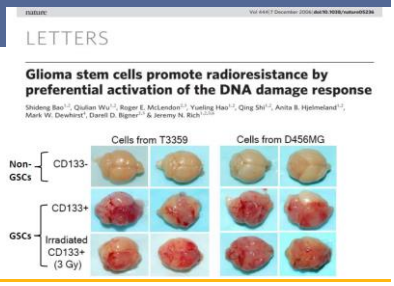




UCLA Health Al-Hajj et al., PNAS 2003. Ginestier et al., Cell Stem cell 2007 6

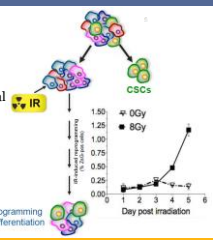
Radioresistance

- Bao et al. Nature 2006

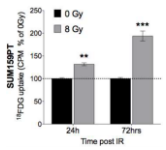


Radiation-Induced reprogramming of non-stem differentiated cancer cells into CSC

- Irradiation on isolated non-stem cancer cell population
  - Reprogrammed CSC population proportional to radiation dose
- Observed in multiple tumor types
  - Breast[1][2]
  - Glioma[3]
  - Head & Neck[4]



Increase in glucose uptake with reprogramming



[1] Lagadec et al., Stem Cells 2012 [2] Vlashi et al., Breast cancer res. & trmt 2014
[3] Vlashi et al., IJROBP 2016

Mathematical modeling of CSC dynamics

- Utilize mathematical models to describe the complex characteristics of CSC and the dynamic interaction between CSC and non-stem DCC
- Mathematical models allow for exploration and optimization of dose fractionation schedules

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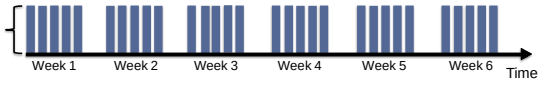

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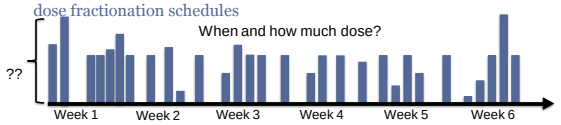
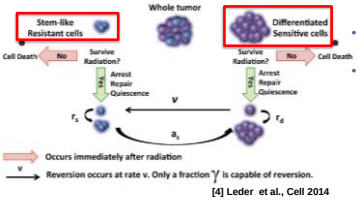


Mathematical Model of CSC Dynamics



[4] Leder et al., Cell 2014

- CSC + non-stem differentiated cancer cells (DCC)[1][2]
- CSC governs cancer progression
  - Higher proliferative capacity through self-renewal
  - Radio-resistant
  - Irradiated DCCs reprogram to CSC[3]

[1] Reya T et al., Nature 2001 [2] Clarke MF et al., Cancer Res 2006
[3] Lagadec C et al., Stem Cells. 2012 [4] Leder et al., Cell 2014

Biological model with CSC

- Development of a biological radiotherapy treatment response modeling with CSC characteristics
  - Dual compartment Linear Quadradic Model (DLQ)

Incorporating Cancer Stem Cells in Radiation Therapy Treatment Response Modeling and the Implication in Glioblastoma Multiforme Treatment Resistance

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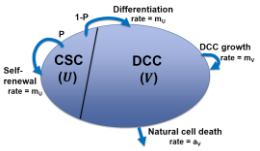
ODE model: interplay of CSC and DCC



Self-Renewal

$$\dot{U}(t) = (2P-1)m_U k(W(t))U(t)$$

Differentiation from CSC

$$\dot{V}(t) = 2(1-P)m_U k(W(t))U(t) + m_V k(W(t))V(t) - a_V V(t)$$

DCC Growth **DCC natural cell death**

$$W(t) = U(t) + V(t)$$

$$K(W) = \max\{1 - W^4, 0\}$$

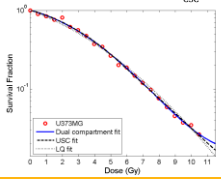
- P = probability a CSC gives rise to two CSC
- 1-P = probability CSC differentiates
- m_U = CSC growth rate, m_V = DCC growth rate, a_V = DCC natural cell death rate
  - Based on potential doubling time of different tumors

Bachman JW et al., Front Oncol 2013; 3:52.
Hillen, T et al., Bull Math Biol. 2013;75:161-84
Yu VY et al., Int J Radiat Oncol Biol Phys 2015 14

Determining radiosensitivity parameters with dual-compartment LQ model

$$SF(D) = F \cdot \exp\{-\alpha_{CSC}D - \beta_{CSC}D^2\} + (1-F) \cdot \exp\{-\alpha_{DCC}D - \beta_{DCC}D^2\}$$

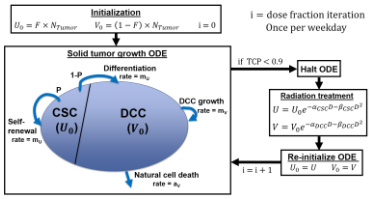
F = 0.016, α_{CSC} = 0.01, β_{CSC}=1.77E-7, α_{DCC} = 0.125, β_{DCC}= 0.028



- Linear-Quadratic (LQ) model incorporating radiological parameters for CSC and DCC
- Curve fitting to published clonogenic survival data of 7 human cell lines

Yu VY et al., Int J Radiat Oncol Biol Phys 2015 15

Simulation



- Fractional doses 2 Gy – 14.3 Gy

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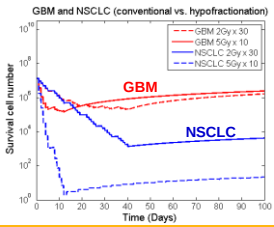
GBM & NSCLC comparison

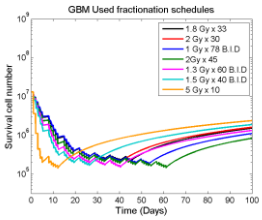


- Model predicts poor GBM response for conventional ***and*** hypo-fractionated[1] treatments
- Hypo-fractionation achieves dramatically better tumor control for NSCLC[2]
  - 3 year survival
    - Conventional: 20-35%[3]
    - Hypo-fractionation: 55.8%[2]
- Both observations coincide with clinical outcomes

UCLA Health

[1] Floyd NS et al., IJROBP 2004 [2] Timmerman R et al., JAMA 2010
[3] Kaskowitz L et al., IJROBP 1993

GBM historically tested fractionation schemes



- Varying treatment schedules
  - Different rates of cell killing
  - But eventual recurrence
- Consistent with clinical observations of high local recurrence rates
- **Model can be used as a platform for FSO exploration**

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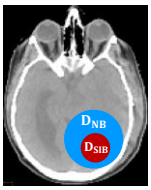
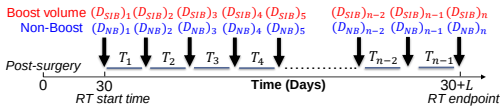
Compartmental FSO

- Heterogeneous tumor containing subvolume with higher tumor proliferation or aggressiveness
  - Simultaneous integrated boost (SIB)
- Optimize fractionation schedule with two different doses at each fraction
  - D_{NB} = dose to non-boost volume
  - D_{SIB} = dose to boost volume



Problem Setup

- Variables
  - Dose fraction sizes: D_{SIB} D_{NB} (length n)
  - Time interval between fractions: T (length n-1)



- Assign total treatment course duration: L
- Fixed number of dose fractions: n

Radiation-induced cell reprogramming

- Based on evidence suggesting DCC reprograms back into CSC after radiation exposure
  - Reprogramming rate proportional to dose received[1][2]
- Linear-Quadratic Radiation killing[3] + cell reprogramming

$$U(t) = U_0 \exp\{-\alpha_{CSC}(D)_i - \beta_{CSC}(D)_i^2\} + \textbf{Reprogramming}$$

$$V(t) = V_0 \exp\{-\alpha_{DCC}(D)_i - \beta_{DCC}(D)_i^2\} - \textbf{Reprogramming}$$

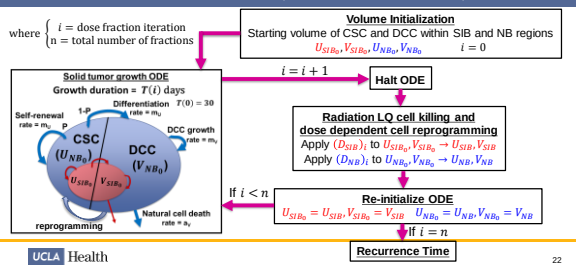
$$\textbf{Reprogramming} = c \cdot (D)_i \cdot V_0 \exp\{-\alpha_{DCC}(D)_i - \beta_{DCC}(D)_i^2\}$$

Linear reprogramming coefficient

Dose dependence

[1] Lagadec C et al., Stem Cells. 2012;30:833-44. [2] Bleau AM et al., Cell Stem Cell. 2009;4:226-35.
[3] Fowler JF et al., Br J Rad 1989

FSO outcome definition (Recurrence Time)



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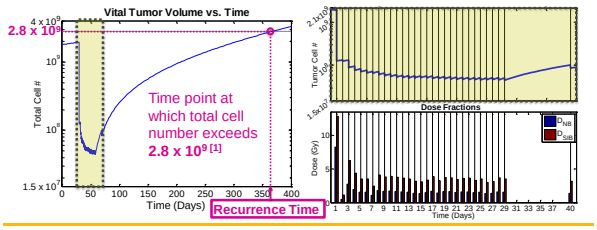


[1] Marko NF et al., J Clin Onc. 2014

Optimization problem constraints

$$\underset{D_{SIB}, D_{NB}, T}{\operatorname{argmax}} \ \text{Recurrence Time}(D_{SIB}, D_{NB}, T)$$

subject to $\sum_{i=1}^{n} (D_{SIB})_i + \frac{(D_{SIB})_i^2}{\alpha/\beta} \leq \text{BED}_{SIB}$ $\sum_{i=1}^{n} (D_{NB})_i + \frac{(D_{NB})_i^2}{\alpha/\beta} \leq \text{BED}_{NB}$

$D_{min} \leq D_{SIB}, D_{NB} \leq D_{max}$, $\sum_{i=1}^{n-1} T_i = L$, $L_s \leq T \leq L$,

$\frac{1}{r} \leq \frac{(D_{SIB})_i}{(D_{NB})_i} \leq r$ $for\ i = 1..n$

- Biological effective dose to both compartments. $\alpha/\beta = 3$
- L = Total treatment duration

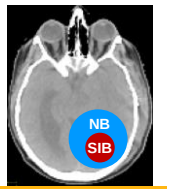
Yu V, UCLA Dissertation 2017

Patient-specific biological models

- Individual patient time to recurrence (n = 7)
- Actual received dose fractionation scheme
  - 1.8 Gy × 33
  - 2 Gy × 30
- Fit original ODE + radiation killing and reprogramming model
  - Initial number of viable tumor cells (N_V)
  - Potential doubling time

Patient-specific SIB

- Non-boost volume (NB)
  - Original planning target volume (PTV) receiving dosage identical to original prescription
- Simultaneous integrated boost (SIB)
  - Derived from eventual recurrence volume
  - Transferred to original planning CT via rigid registration
  - 3 mm expansion of transferred volume



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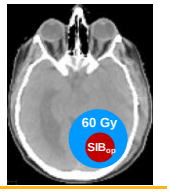
  - Transferred to original planning CT via rigid registration
  - 3 mm expansion of transferred volume
- **Solve achievable SIB dose (SIB_{op}) with 4π optimization formulation maximizing SIB dose**



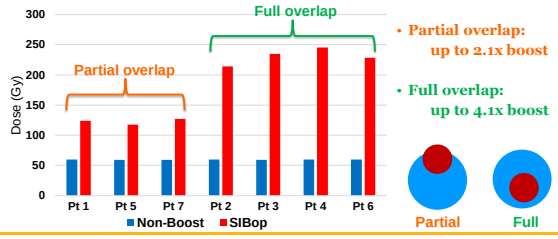
Fractionation schedule optimization

- Volume initialization
  - SIB volume with higher concentration of CSC
  - Study the potential benefit from wide range of concentrations
    - m = CSC concentration enhancement multiplier in SIB
    - R = volume fraction of SIB out of total treated volume

$$R = \frac{SIB}{SIB \cup NB} \quad \text{(case-specific)}$$

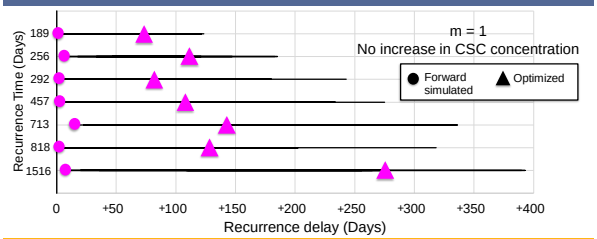
Tested m = 1, 2, 5, 10

4π SIB boost doses



- Partial overlap: up to 2.1x boost
- Full overlap: up to 4.1x boost

Personalized FSO



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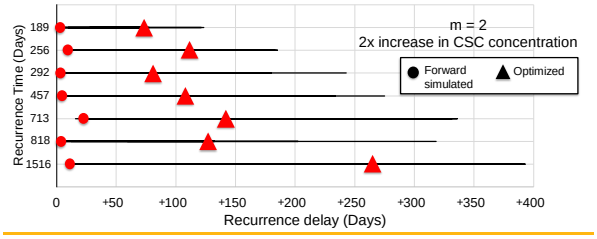

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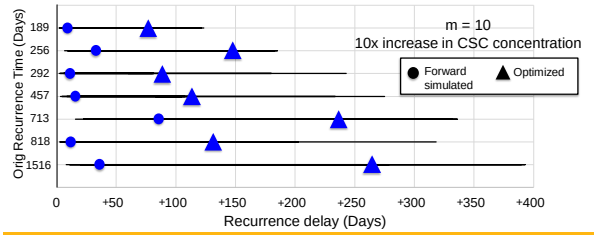
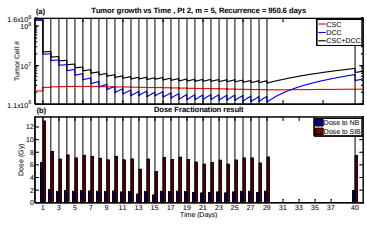
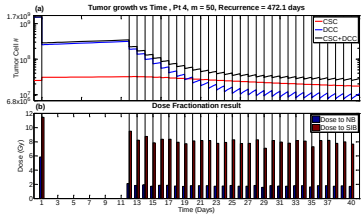


Personalized FSO (Type 1)



- Large fraction in beginning
- Relatively similar doses for the remaining fractions
- Dense once per day treatment in the beginning
- Long time interval in the end

Personalized FSO (Type 2)



- Observed for larger m
- Large fraction in beginning
- Relatively similar doses for the remaining fractions
- Long time interval after first fraction
- Dense once per day treatment in the end

GBM preclinical modeling and validation

Mathematical Modeling of PDGF-Driven Glioblastoma Reveals Optimized Radiation Dosing Schedules

Cell

Kevin Leder,[1,9] Ken Pitter,[2,9] Quincey LaPlant,[3] Dolores Hambardzumyan,[3] Brian D. Ross,[4] Timothy A. Chan,[5] Eric C. Holland,[6,7] and Franziska Michor[7,8,*]

[1]Department of Industrial and Systems Engineering, University of Minnesota, Minneapolis, MN 55455, USA
[2]Brain Tumor Center, Department of Cancer Biology and Genetics, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA
[3]Departments of Neurosciences and Molecular Medicines, Cleveland, OH 44195, USA
[4]Center for Molecular Imaging and Department of Radiology, University of Michigan, Ann Arbor, MI 48109, USA
[5]Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA
[6]Division of Human Biology, Fred Hutchinson Cancer Research Center, and Alvord Brain Tumor Center, University of Washington, Seattle, WA 98109, USA
[7]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA 02215, USA
[8]Department of Biostatistics, Harvard School of Public Health, Boston, MA 02215, USA

GBM preclinical modeling and validation

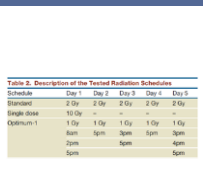
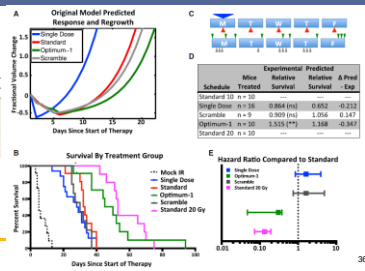


Table 2. Description of the Tested Radiation Schedules

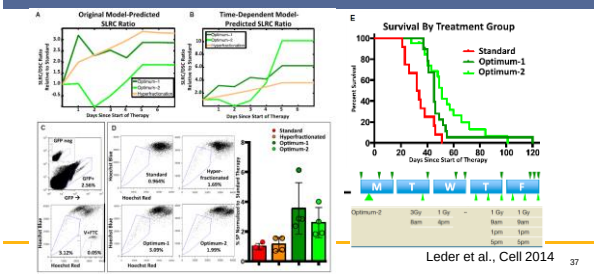
Schedule	Day 1	Day 2	Day 3	Day 4	Day 5
Standard	2 Gy	2 Gy	2 Gy	2 Gy	2 Gy
Single dose	10 Gy	–	–	–	–
Optimum-1	1 Gy	1 Gy	1 Gy	1 Gy	1 Gy
	8am	5pm	3pm	5pm	3pm
	2pm		5pm		4pm
	5pm				5pm



Schedule	Mice Treated	Experimental Relative Survival	Predicted Relative Survival	Δ Pred - Exp
Standard 10	n = 10	---	---	---
Single Dose	n = 16	0.864 (ns)	0.652	-0.212
Scramble	n = 9	0.909 (ns)	1.056	0.147
Optimum-1	n = 10	3.535 (**)	3.168	-0.367
Standard 20	n = 10	---	---	---

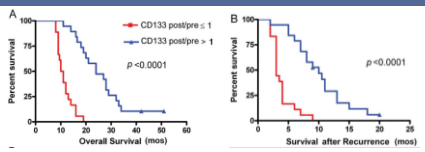
Leder et al., Cell 2014

Second iteration



Leder et al., Cell 2014

GBM Stem cell enrichment (CD133+) associated with increased survival



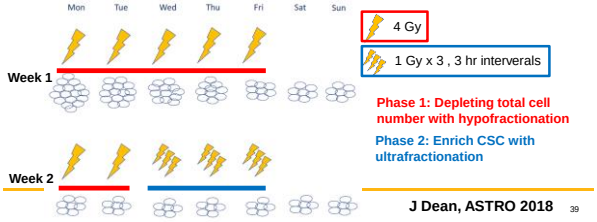
- Stem cell population (CD133+ enrichment has higher replicative potential but are also slower glowing
- Not a good strategy for cure but for GBM patients with poor prognosis, it might be a strategy to delay onset of tumor progression and death

UCLA Health

Pallini et al., Cancer 2011

Ongoing Clinical Trial at Harvard in Recurrent GBM patients (NCT 03557372)

- Non-randomized feasibility study, n = 14
- Optimized treatment schedule, BED equivalent to 35 Gy in 10 fx (RTOG 1205)



J Dean, ASTRO 2018

Conclusion

- Mathematical modeling of CSC dynamics provides insight on treatment strategies
  - Reflected the definitive treatment failure of GBM while demonstrating superior outcome with hypofractiontion in NSCLC
- Treatment fractionation schedule optimization could be further explored to improve treatment outcome
  - Preclinically validated for GBM with ongoing trial in human
- Combination of key radiobiological concepts with mathematical modeling and optimize treatment strategies could make a large impact in improving treatment outcome

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