Optimizing the Dose Fractionation Schedule

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1. Linear-quadratic model (BED) based fractionation optimization:

BED model

Biologically equivalent dose (BED)

(clinical)

$$\mathrm{b} = nd\left(1 + \frac{d}{(\alpha/\beta)}\right)$$

number of fractions

dose per fraction

tissue parameter

$$b = -\log(S)/\alpha$$

Linear-quadratic cell survival

(in vitro)

$$S = \exp\left(-n[\alpha d + \beta d^2]\right)$$

Generalization to non-uniform schedules

$$b = \sum_{t=1}^{n}\left[d_t + \frac{d_t^2}{(\alpha/\beta)}\right]$$

Optimizing BED

Determine optimal fractionation scheme

minimize BED in normal tissue

subject to BED in tumor = prescription

Results:

- uniform fractionation (same dose every day) is optimal
- hypo-fractionation if $\frac{\left(\frac{\alpha}{\beta}\right)_N}{\left(\frac{\alpha}{\beta}\right)_T} > \frac{d_N}{d_T}$
- standard hyper fractionation if $\frac{\left(\frac{\alpha}{\beta}\right)_N}{\left(\frac{\alpha}{\beta}\right)_T} < \frac{d_N}{d_T}$

Non-uniform dose distributions (parallel organs)

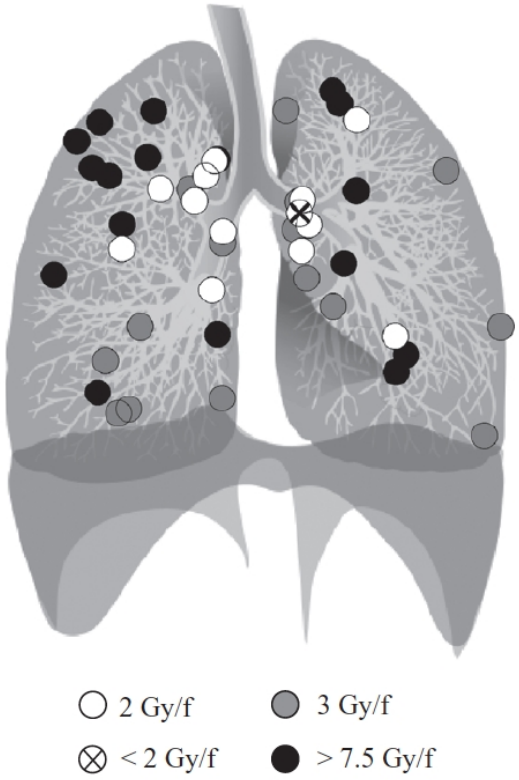
sparing factor $d = \frac{d_N}{d_T} = \frac{\text{Dose to critical structure}}{\text{Dose to tumor}}$ (Mizeutatla

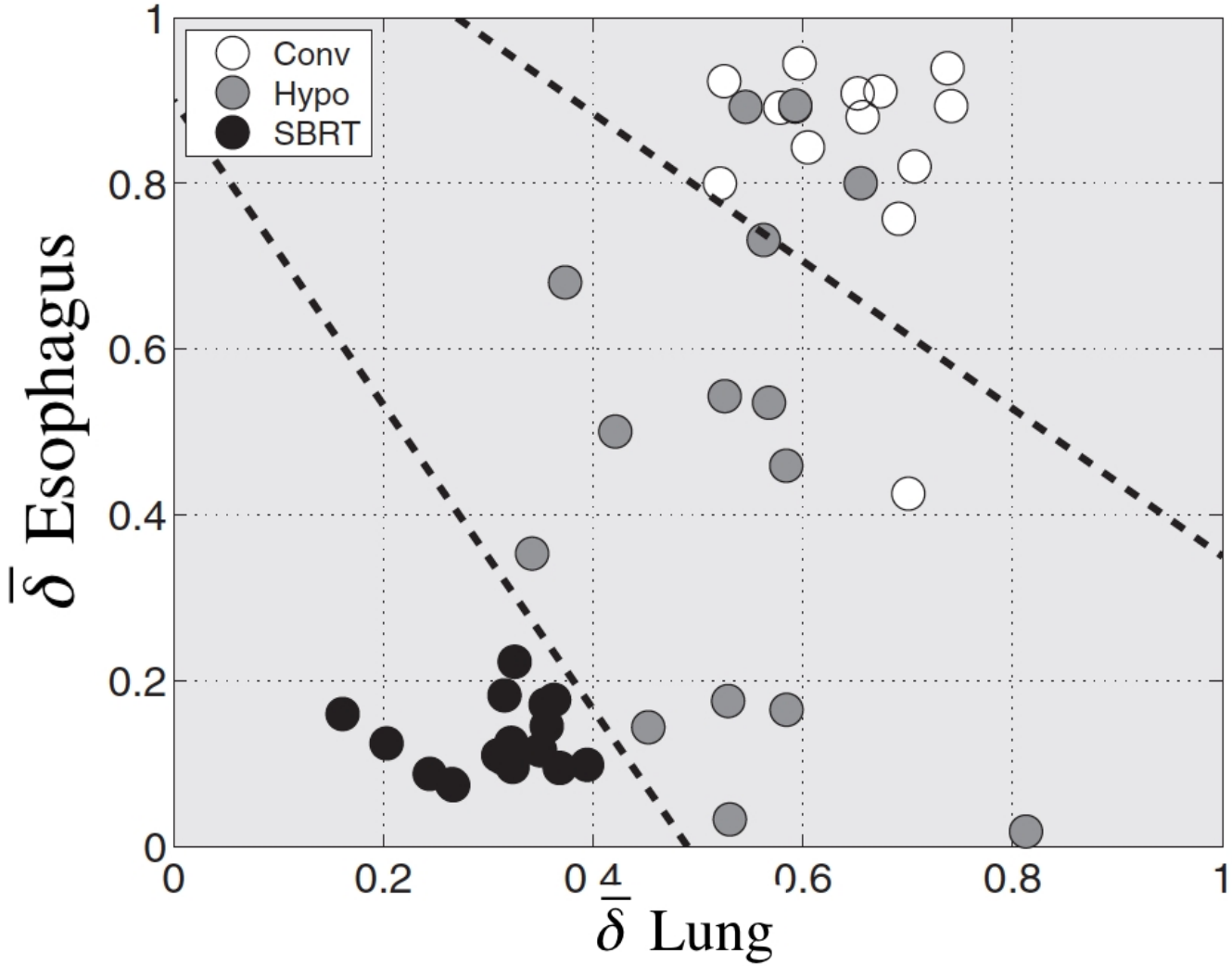
effective sparing factor $d = \frac{\sum_i d_i^2}{\sum_i d_i}$ (Unkelebaal P.M, 2 0 1
(Kedal lMre, Phy 2 s 1

If $\frac{[a/b]_N}{[a/b]_T} > d$ then *hypo*-fractionation is optimal.

If $\frac{[a/b]_N}{[a/b]_T} < d$ then *hyper*-fractionation is optimal.

Results from 46 lung (NSCLC) patients





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Keller et al., Med Phys 40(8), 2013

2. Optimizing the Combined spatial and temporal dose distribution:

Spatio-temporal fractionation schemes

What would be ideal?

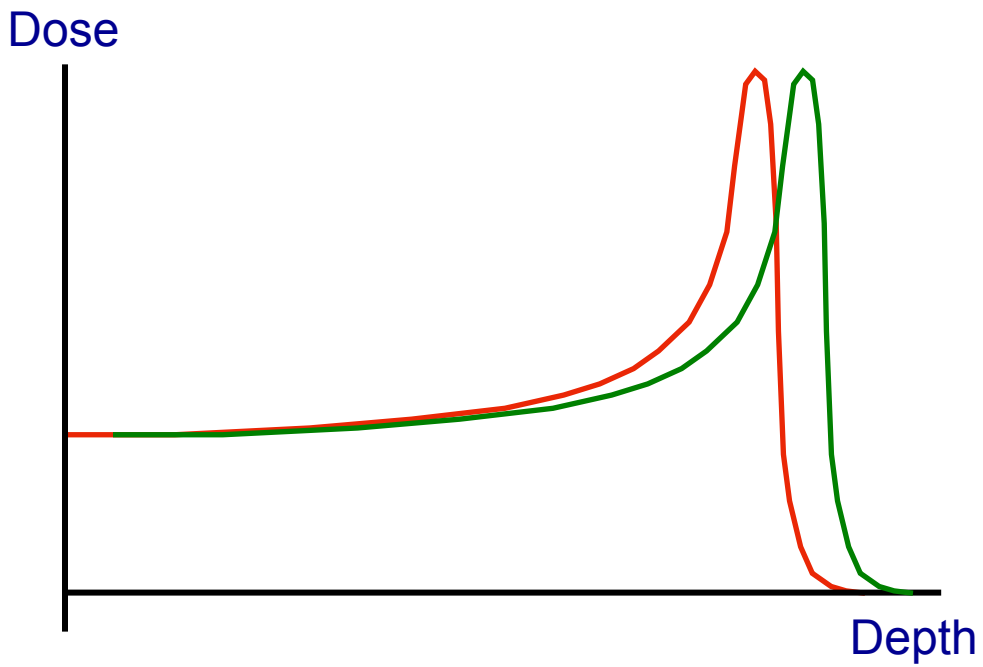
Fractionate in normal tissues **AND** hypofractionate in the tumor

Unkelbach and Papp, Medical Physics, 42, 2234 (2015)

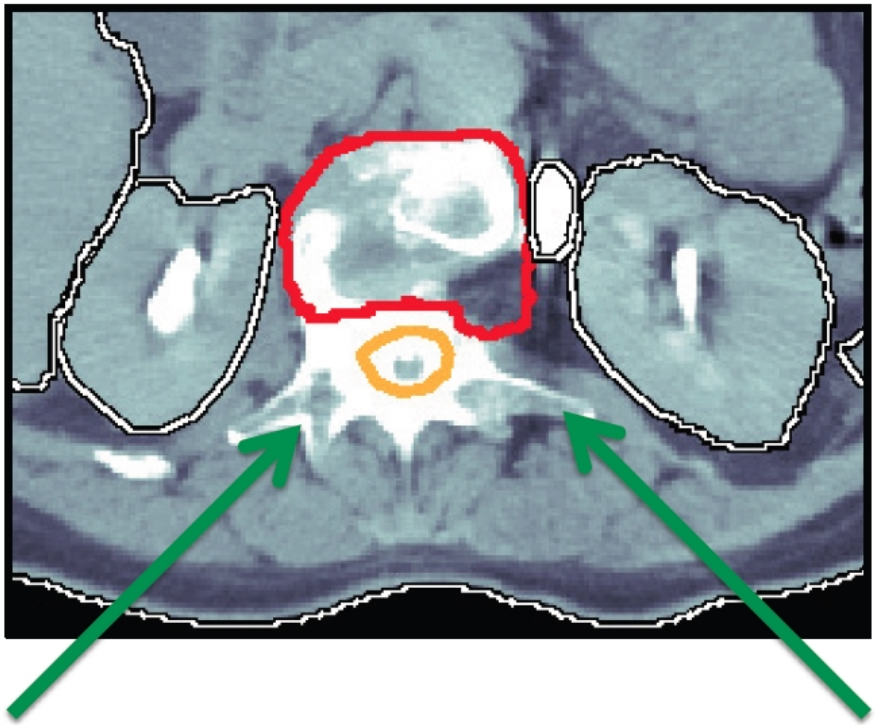
Best in physics award, AAPM 2013

Example: Proton therapy (works also with x-rays)

- the entrance dose is almost independent of the range of the proton beam



Example
Spinal metastasis treatment, two beams



Objective function:

$$
\begin{aligned}
f(b) \;=\; & \frac{10}{N_T}\sum_{i\in T}(b^{pres}-b_i)_+^2 \\
+\; & \frac{1}{N_T}\sum_{i\in T}(b_i-b^{pres})_+^2 \\
+\; & \frac{1}{N_K}\sum_{i\in K} b_i \quad \text{kidney} \\
+\; & \frac{1}{N_S}\sum_{i\in S} b_i \quad \text{spinal cord} \\
+\; & \frac{1}{N_H}\sum_{i\in H} b_i \quad \text{healthy tissue}
\end{aligned}
$$

BED based treatment planning

General problem formulation:

$$\begin{aligned}
&\underset{x}{\text{minimize}} && f(\boldsymbol{b}) && && \text{objective function evaluated for cumulative BED}\\
&\text{subject to} && c_k(\boldsymbol{b}) \leq u_k && \forall k &&\\
& && b_i = \sum_{t=1}^{n} b_{ti} && \forall i && \text{cumulative BED}\\
& && b_{ti} = d_{ti} + \left(\frac{\beta}{\alpha}\right)_i d_{ti}^2 && \forall i,\ \forall t && \text{BED in fraction t}\\
& && d_{ti} = \sum_j D_{ij} x_{tj} && \forall i,\ \forall t && \text{physical dose}\\
& && x_{tj} \geq 0 && \forall j,\ \forall t && \text{positivity of beam intensities}
\end{aligned}$$

Example
Spinal metastasis treatment, two beams

Optimize single plan

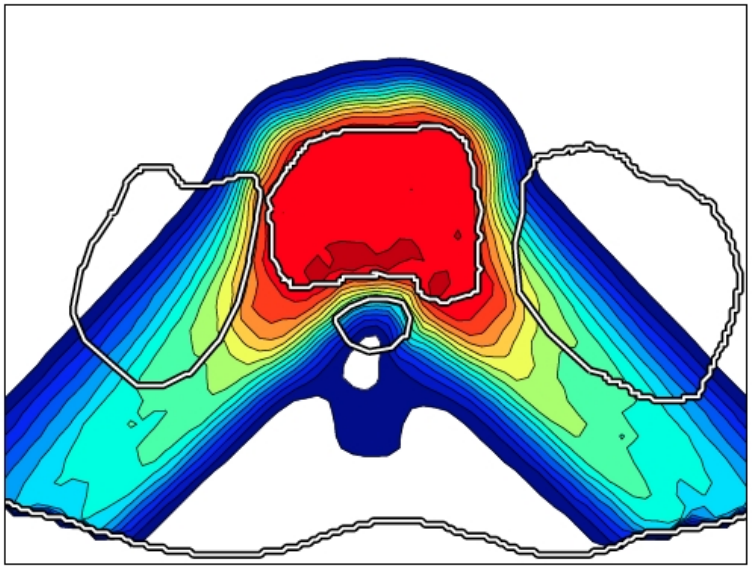
Parameters

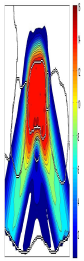
- two fractions (hypofractionated regimen)
- α/β ratios: tumor = 10, spinal cord = 2, normal tissue = 4
- prescribed BED = 72 Gy (30 x 2Gy)
- physical dose per fraction = 14.6 Gy
- maximum BED constraint on spinal cord (13.6 Gy in two fractions)

Optimization

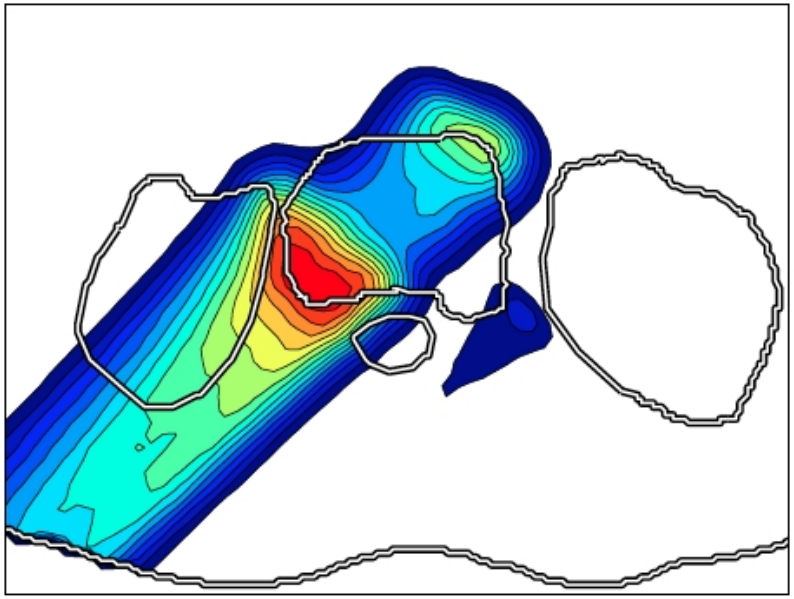
- L-BFGS quasi-newton method

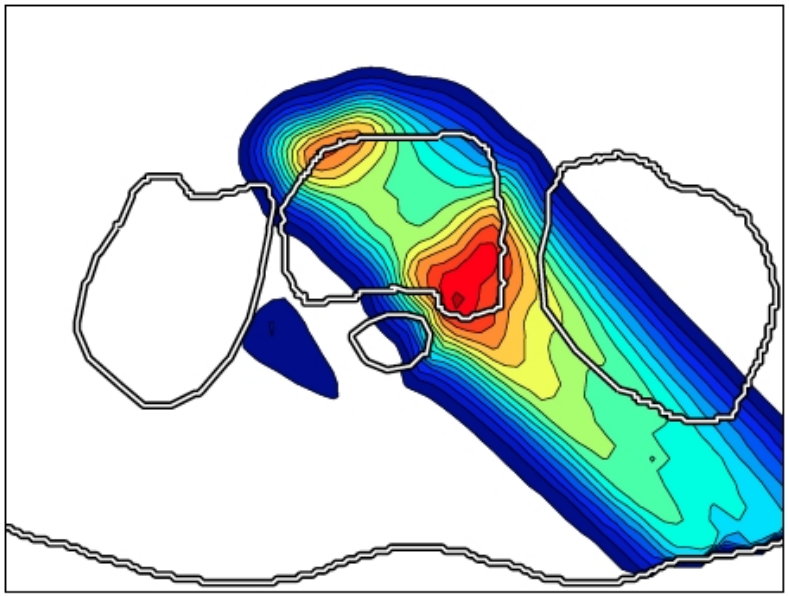
Uniform reference plan (same dose every day)





physical dose per fraction





Non-uniform plan

Optimize two fractions simultaneously

- focus on improving kidney dose
- use constrained formulation

$$\underset{x}{\text{minimize}} \quad \frac{1}{N_K}\sum_{i\in K} b_i$$

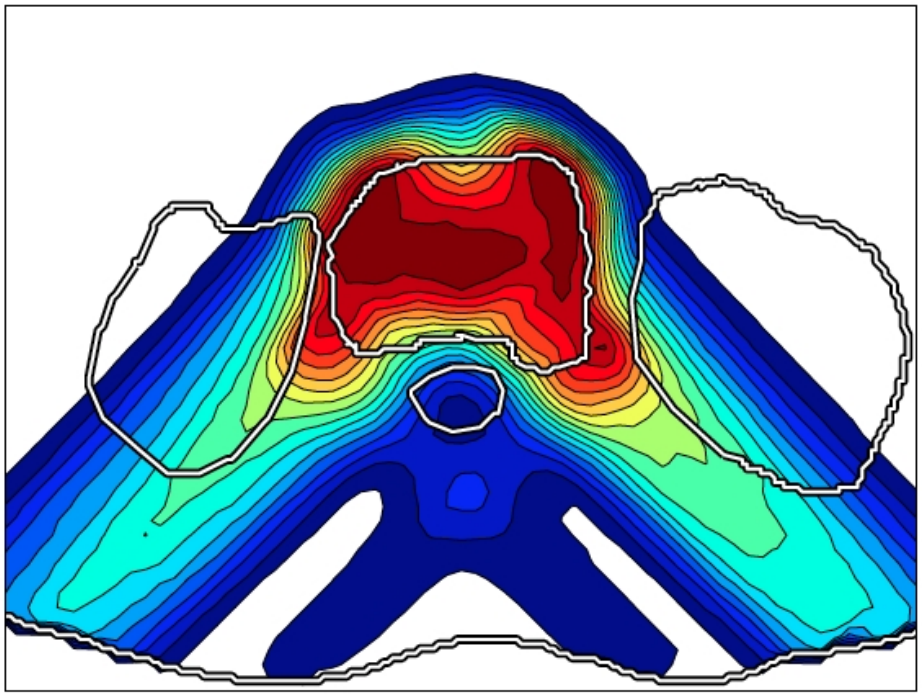
minimize kidney mean BED

$$\begin{aligned}
\text{subject to} \quad & \frac{10}{N_T}\sum_{i\in T}(b^{pres}-b_i)_+^2 + \frac{1}{N_T}\sum_{i\in T}(b_i-b^{pres})_+^2 \leq f_T^* \\
& \frac{1}{N_S}\sum_{i\in S} b_i \leq f_S^* \\
& \frac{1}{N_H}\sum_{i\in H} b_i \leq f_H^*
\end{aligned}$$

constraints on tumor, spinal cord, healthy tissue (based on reference plan)

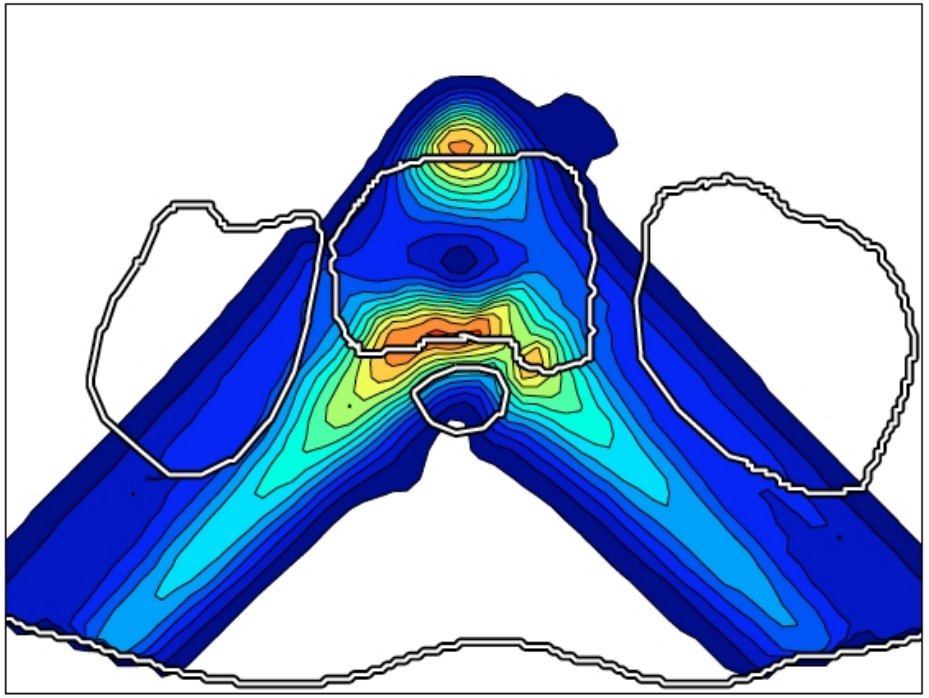
Non-uniform plan

Optimize two fractions



Fraction 1

(physical dose)



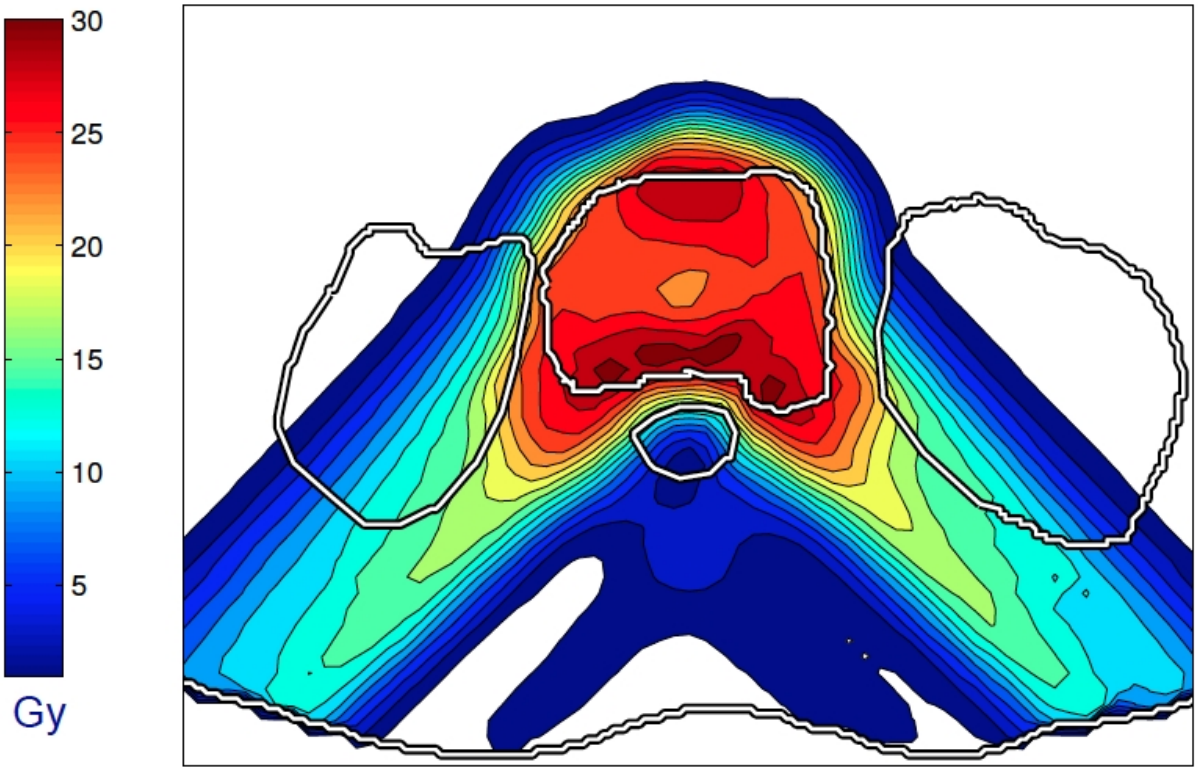
Fraction 2

(physical dose)

Non-uniform plan

Total physical dose is inhomogeneous

(Homogeneous prescribed BED in the target)

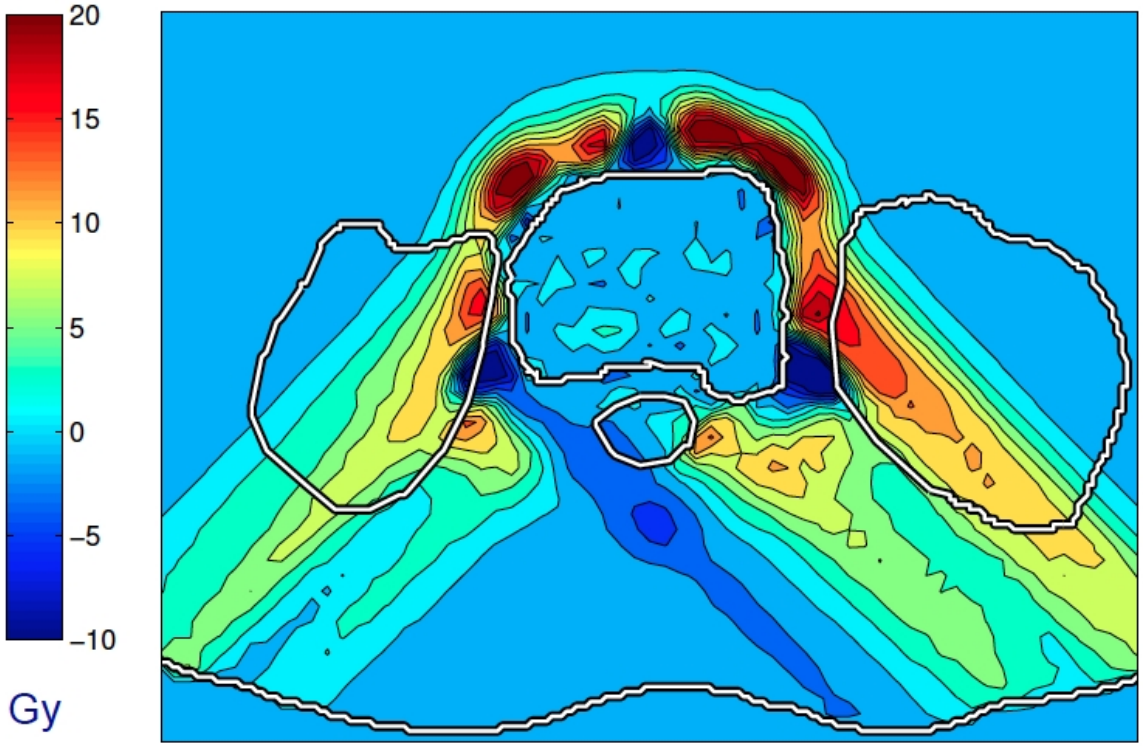


- Hypofractionation in the center allows for reduction in physical dose

Plan comparison

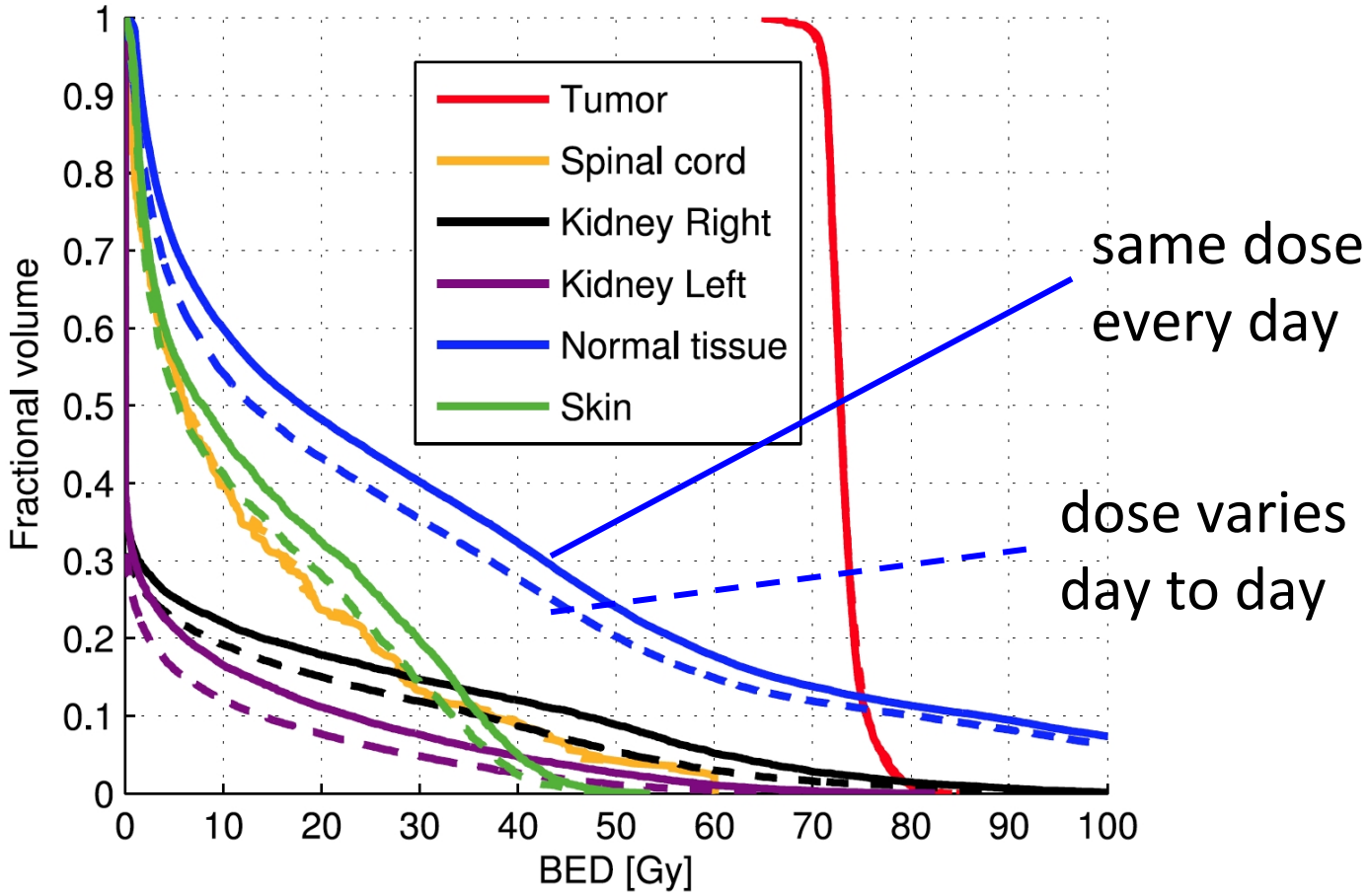
Difference in BED

(Reference plan – non-uniform plan)



- reduced BED in entrance region
- kidney mean dose reduced by 25 %
- Skin mean dose reduced by 13 %

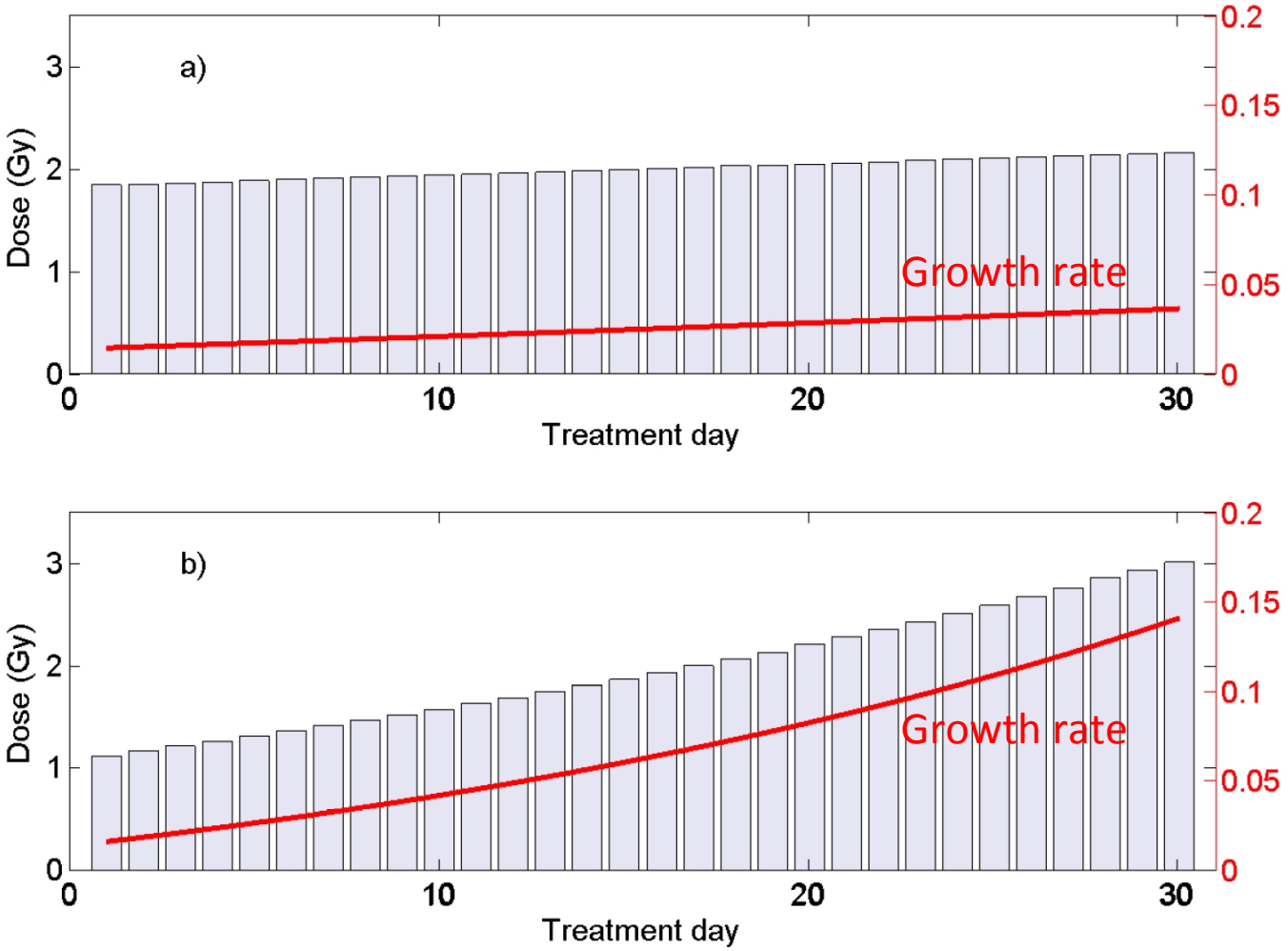
Results: DVH


Tumor
Spinal cord
Kidney Right
Kidney Left
Normal tissue
Skin
Fractional volume
BED [Gy]
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
10
20
30
40
50
60
70
80
90
100
same dose every day
dose varies day to day

What we learnt so far

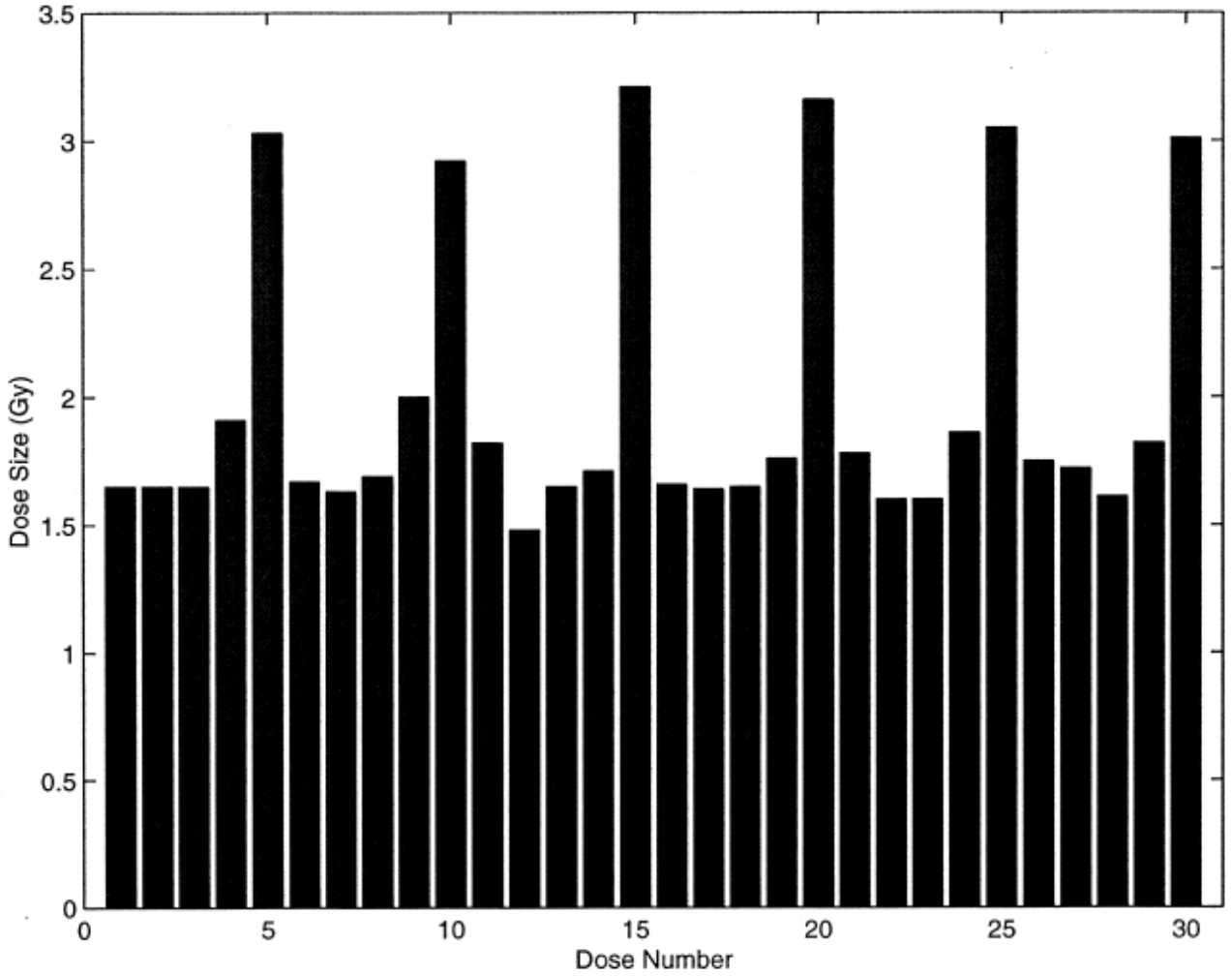
3. Including re-population:

Variation of dose over treatment course (with accelerated repopulation)



Ramakrishnan et al., Informs J of Computing, 2015

More dose on Fridays?
Model with repopulation



Wein et al., IJROBP 2000

4. Combined modality (chemo-radiation) scheduling

Concurrent chemoradiation

Consider impact of chemotherapy on fractionation decisions

$$b = \sum_{t=1}^{n} \left[d_t + \frac{d_t^2}{(\alpha/\beta)} + \eta c_t + \zeta c_t d_t \right]$$

Extended BED model

additive effect

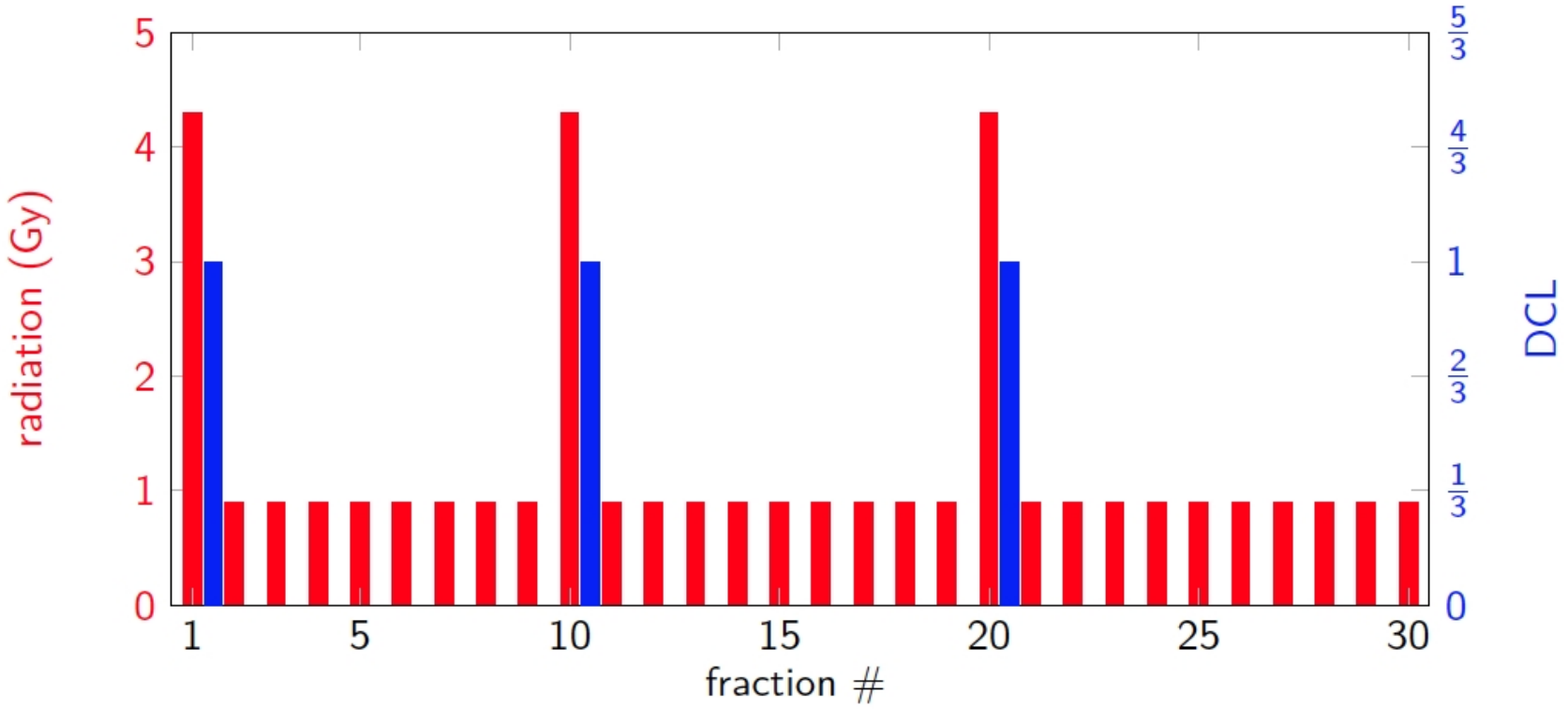
radiosensitization

Consider drug with these properties:

- good radiosensitizer in the tumor
- bad additive effect in normal tissue

⍰ gives rise to non-uniform fractionation schemes

Concurrent chemoradiation



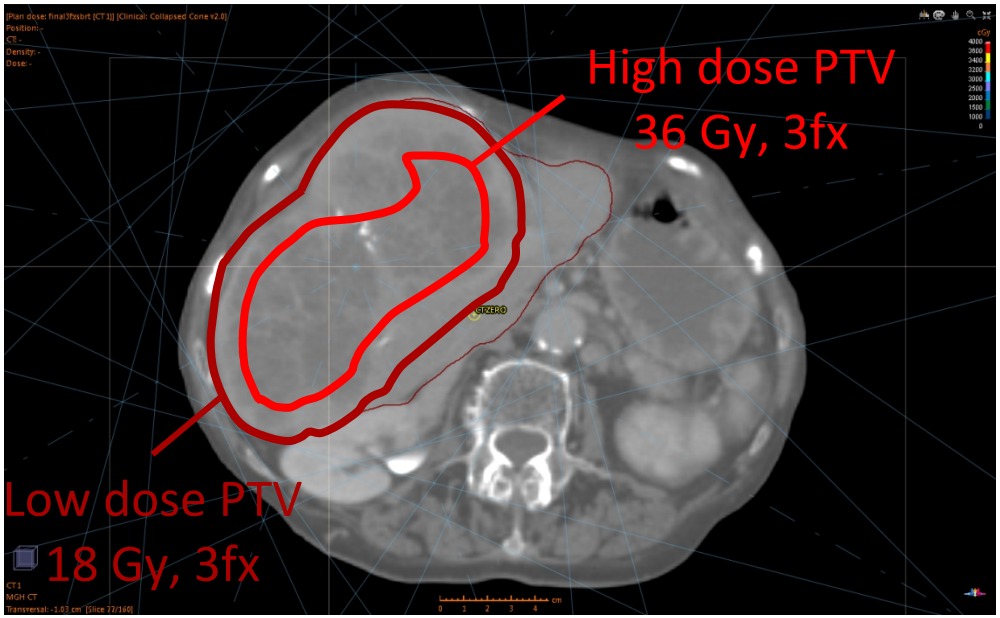
- avoid drug due to toxic effect on normal tissue
- capitalize on radiosensitizing effect in a few boost fractions

Salari et al., IIE Healthcare 2015, in press
Focus Highlight article

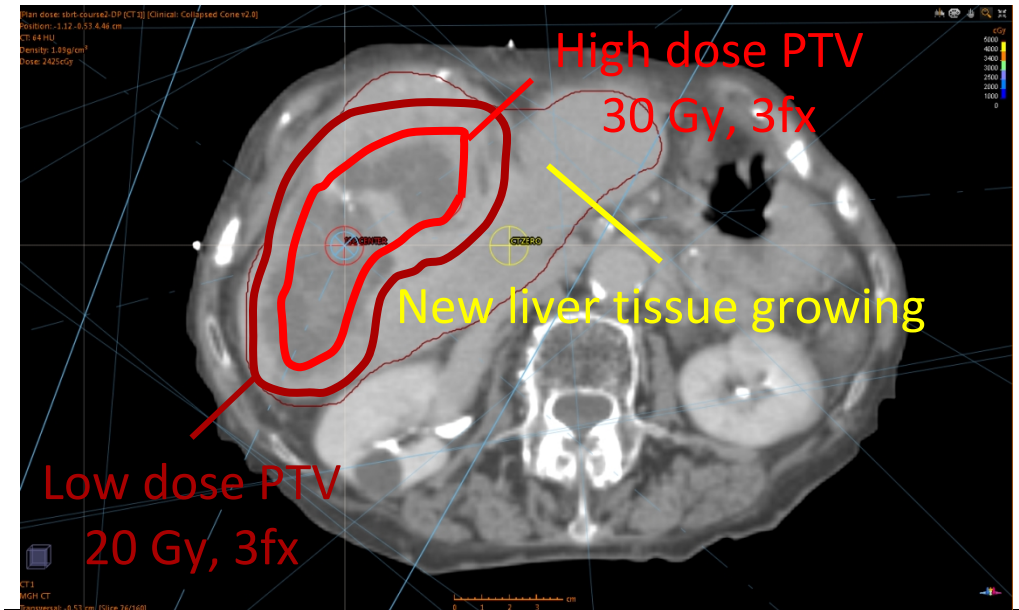
5. Re-discovering split-course treatments:

Re-discovering split course therapy

1st phase
(December 2012)



2nd phase
(April 2013)



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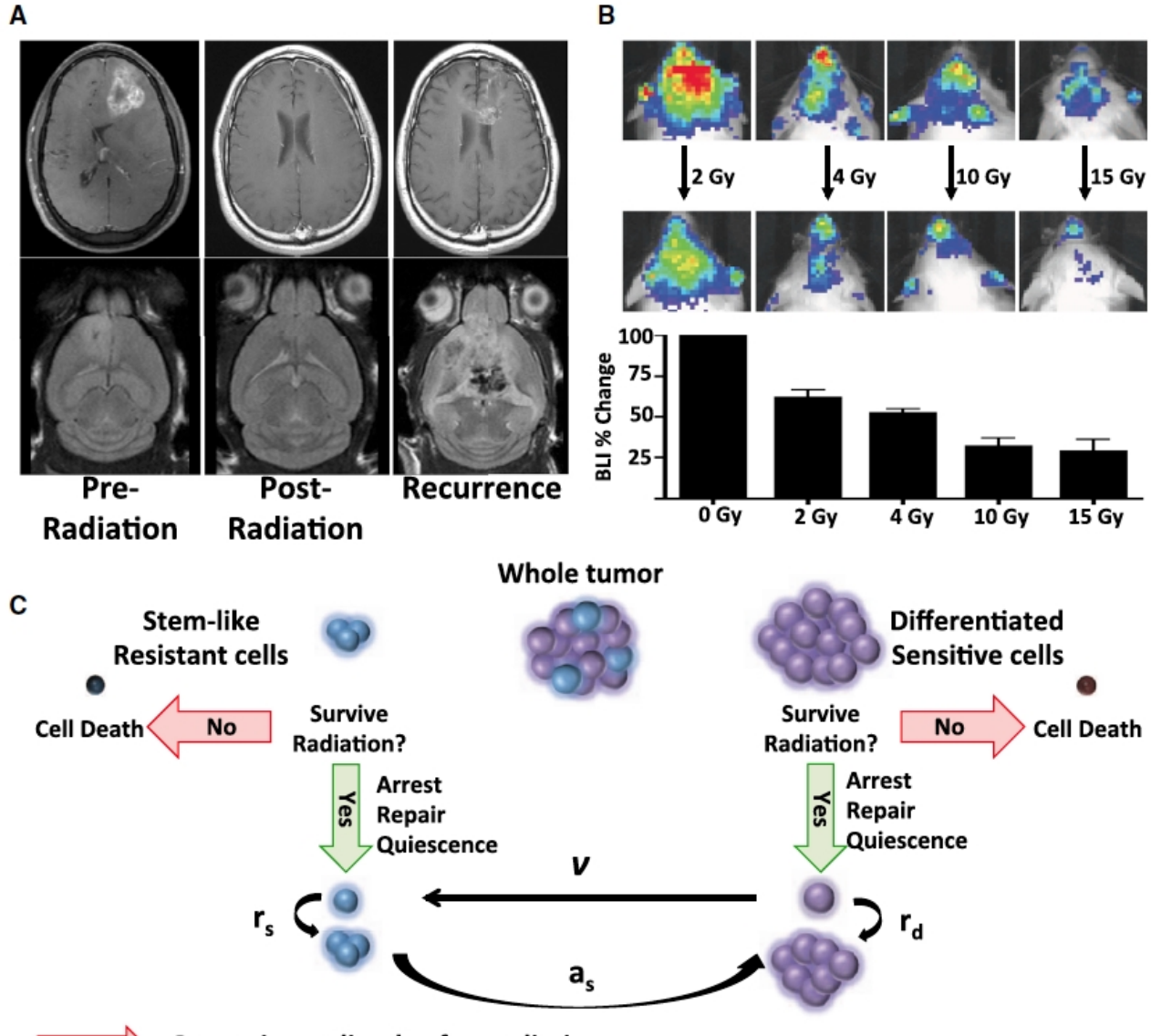
Split course for liver
Change in volumes (cc)

	Liver – CTV	CTV
Phase 1	723	1218
Phase 2	753	499

This approach allows one to reduce overall BED in healthy liver by more than 50%.

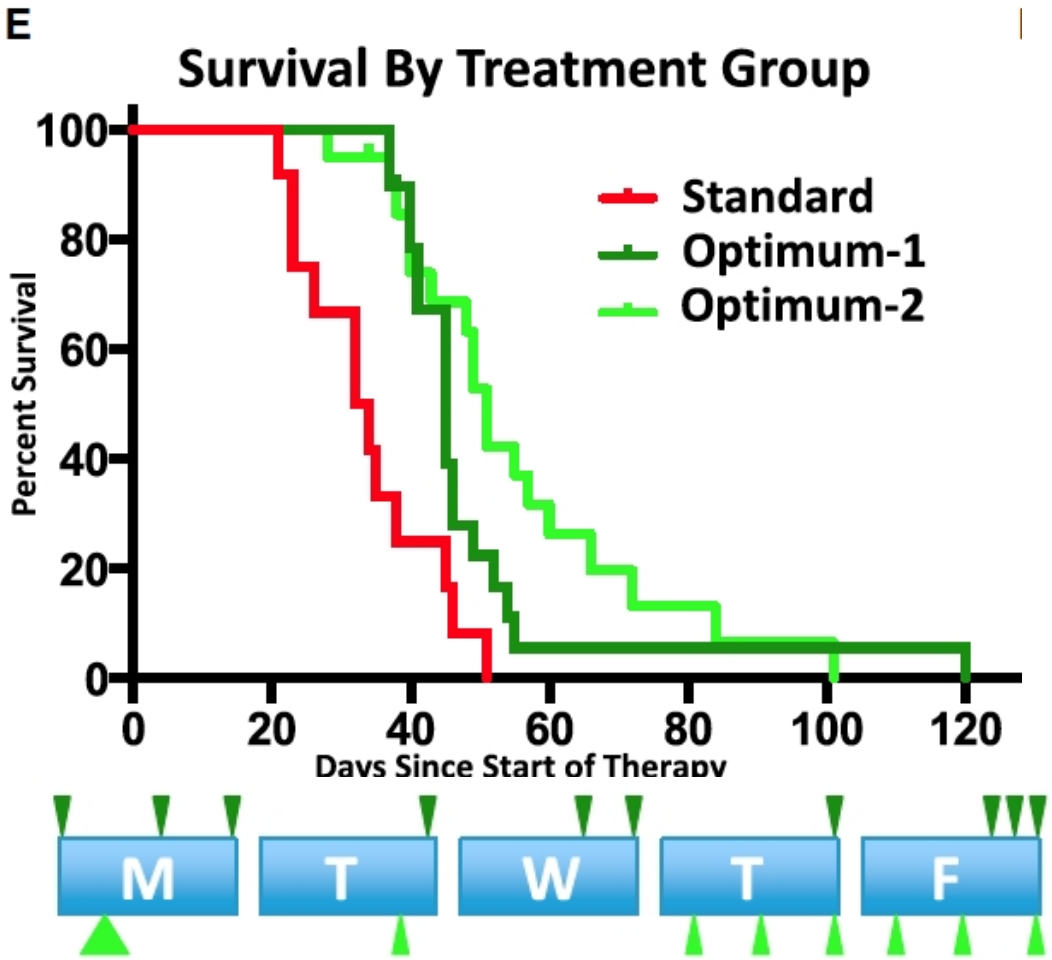
6. Genetic model based fractionation optimization:

Fractionation optimization for glioblastoma Stem cell model



Leder et al., Cell 156, 2014

Survival in mouse experiment
10 Gy over 1 week, different fractionation



Leder et al.,
Cell 156, 2014

Optimized dose fractionation…

- … depends on spatial dose delivery
- … calls for *non-uniform* dose per fraction
- … requires optimal scheduling together with other treatment modalities (chemotherapy)

- lots of room for improvement.

Thanks in particular to

Jan Unkelbach, PhD

David Craft, PhD

Ehsan Salari, PhD

Ted Hong, MD

- **the whole team**

Funding:

- NCI
- RaySearch
- Philips

David Papp, PhD

Jagdish Ramakrishnan, PhD

Optimizing BED

Determine optimal fractionation scheme

$$b = \sum_{t=1}^{n} \left[d_t + \frac{d_t^2}{(\alpha/\beta)} \right]$$

Assume a fixed total physical dose:

- for normal tissue it is optimal to split the total dose equally in n fractions (minimizes BED)
- for a tumor it is optimal to deliver all dose in one fraction (maximizes BED)

 inherent trade-off