UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE
DEPARTMENT OF RADIATION ONCOLOGY

SU-F-TRACK 5-0

Clinical Outcomes Modeling

Response Models for Tumor Control

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2020 Improving Health QUALITY. Increasing Global IMPACT.
JULY 12–16 VIRTUAL EASTERN TIME (GMT-4)
JOINT AAPM | COMP MEETING

Outline

- Tumor Control Probability (TCP) Models: Poisson and beyond.
- Basic Linear-Quadratic (LQ) model
- Rationale for Fractionation and optimization of fractionation schedules
- Example of LQ model parameter derivation
- LQ model with additional “Rs”

(Repopulation, Reoxygenation and Redistribution)

- Biologically Adaptive Therapy

(Example for Head and Neck Dose-painting)

- Current Challenges and Future Directions

Tumor Control Probability (TCP)
Why use Poisson?

-Start with two basic principles:

- Goal is to damage ALL cancer cells to prevent them from proliferation
- Random nature of cell killing due to radiation

It follows that

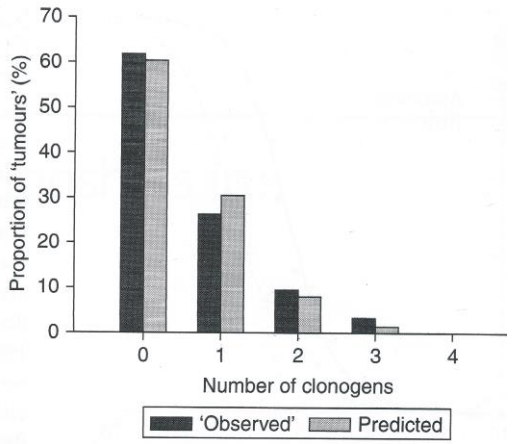
Probability of cure depends on average number of surviving clonogens

(Munro and Gilbert 1961 milestone article)

Random Nature of cell killing TCP=Poisson distribution

- Consider an ensemble of 100 tumors with N_0 identical cells
- Radiation effect random process with average number of surviving clonogens $\langle S_c \rangle$ (=0.5 here)
- Monte Carlo simulation shows each tumor (a square in the figure) with a certain number of surviving clonogens
- Number of surviving clonogens is Poisson distributed

0	0	0	2	1	1	1	0	0	0
0	0	0	0	0	0	0	0	1	0
0	0	0	2	1	2	1	2	0	1
1	0	0	0	0	2	1	0	1	2
1	2	0	0	0	0	0	0	0	3
0	0	0	0	0	0	0	1	1	0
1	0	2	0	0	0	0	0	0	1
0	0	0	0	0	3	0	0	1	0
0	3	1	1	1	1	0	0	0	1
0	1	2	1	1	0	0	1	1	0



from Bentzen 2009

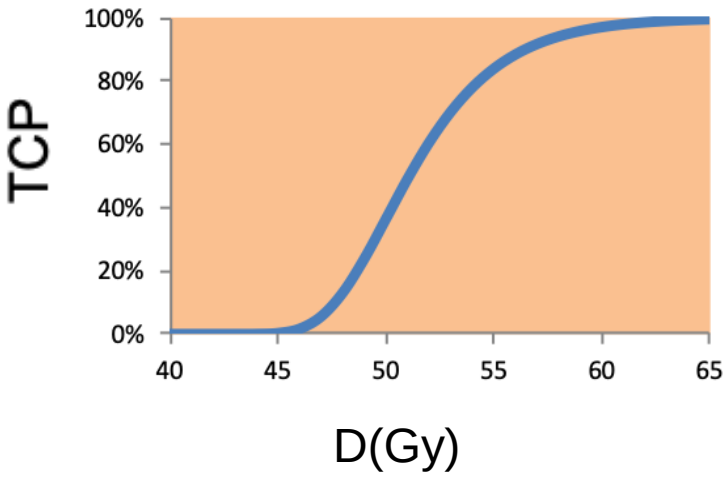
Tumor Control Probability (TCP) Poisson distribution

- Tumor control probability is the probability of zero surviving clonogens (zero order term of Poisson distribution)

$$\text{Poisson } TCP = e^{-\langle S_c \rangle}$$

$\langle S_c \rangle$=Average Number of surviving clonogens after radiation

If $\langle S_c \rangle \sim \exp(-\alpha D)$ TCP a sigmoid function of D



Ref: -Munro and Gilbert 1961
-S. Bentzen 2009 in "Basic Clinical Radiobiology"

TCP but not Poisson
Several alternatives

- Logistic dose response model:

  -Pragmatic, non-mechanistic, widely used in biology
  -Uses standard statistics software
  -Can give an estimate of some biological parameters
  -Advantage: terms representing additional patient characteristics can be included

- Zaider-Minerbo model

  -Mathematical model based on birth-death stochastic processes
  -Mechanistic-based but more complicated formulas

- …

from Bentzen 2009, Zaider and Minerbo(2000)

Poisson $TCP = e^{-<S_c>=N_0<S>}$

Next big decision: How to describe <S> vs. D

- Linear-Quadratic (LQ) Model Survival Fraction

$$S = e^{-\alpha D - \beta G D^2}$$

$$G = \frac{2}{D^2}\int_{-\infty}^{\infty}\dot{D}(t)dt\int_{-\infty}^{t}e^{-\mu(t-t')}\dot{D}(t')dt'$$

- Two components of cell-killing, one linear (α), one quadratic (β)
- G is the Lea-Catcheside dose-protraction factor with $\mu = \ln(2)/T_{rep}$ with T_{rep} the characteristic repair time
- G accounts for the temporal characteristics of the dose delivery
- Not just simple Taylor expansion given G
- LQ is the low dose, low dose-rate approximation of SEVERAL kinetics models like the Lethal-Potentially-Lethal (LPL) and others

Lea-Catcheside factor G accounts for dose protraction (G≤1)

- $G = 1$ for acute single dose (treatment time T << T_{rep}, no time for repair)

$$S = e^{(-\alpha D - \beta D^2)}$$

- $G = 1/n$ for acute single dose (treatment time T << T_{rep}, no time for repair)

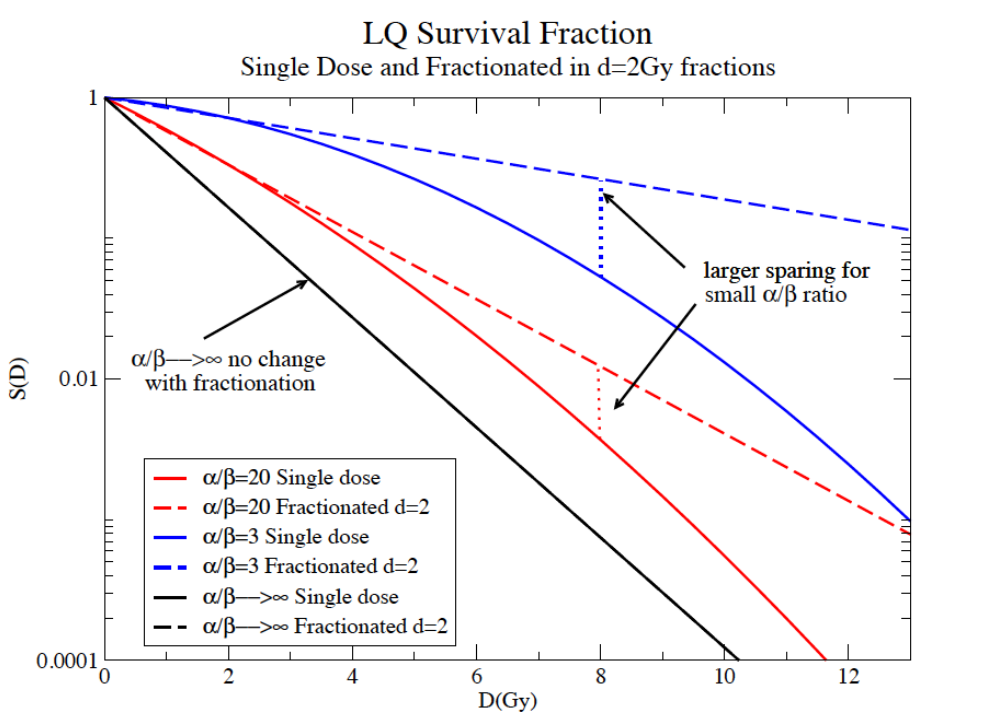
$$S = e^{(-\alpha D \cdot (1 + d/r))} \qquad r = \alpha/\beta$$

- $G = \frac{T_{rep}}{T_{rep} + T_{1/2}}$ for permanent brachytherapy, $T_{1/2}$ is the isotope's half-life
- $G = \frac{2}{(\mu T)^2}(e^{-\mu T} - 1 + \mu T)$ for constant dose-rate D/T
- (T=treatment time, μ=ln(2)/T_{rep}, T_{rep}=characteristic repair time)

What's with the α/β ratio r?
Very important: sensitivity to fractionation

- α/β ratio has units of dose
- α/β ratio equals the dose at which the linear and quadratic terms of the LQ model are the same.
- α/β ratio determines the sensitivity to fractionation
- α/β ratio $\longrightarrow \infty$ the survival curve is a straight line and biological effect is independent of fraction size.
- As the α/β ratio is reduced, fractionation effects come into play

LQ for fractionated RT(G=1/n) Compare to Single Dose



-Fractionation spares with respect to single dose as long as α/β not infinity

-Fractionation spares MORE for lower α/β, increasing the therapeutic ration

LQ model Biological Effect E, BED and EQD2

- Biological effect E can be characterized by minus the log of the survival fraction $E = \alpha D + \beta D^2$
- For fractionated RT $$E = \alpha D\left(1 + \frac{d}{(\alpha/\beta)}\right)$$
- Biologically Effective Dose (BED) is a useful quantity to compare fractionation schedules

$$BED = E/\alpha = D\left(1 + \frac{d}{(\alpha/\beta)}\right)$$

- Equivalent dose in 2Gy(EQD2) is similar to BED, but less sensitive to changes in parameters

$$EQD2 = BED/\left(1 + \frac{2}{(\alpha/\beta)}\right)$$

E. Hall Radiobiology for the radiologist

Why do we fractionate?
Early evidence on α/β ratio values

- Results from in-vivo animal experiments showed

  -Early-responding tissues(tumors)→large *α/β* ratio~10Gy
  -Late-responding normal tissues →small *α/β* ratio~3Gy

- Early clinical experiences showed advantage of fractionation and hyperfractionation in the reduction of late effects for a dose with the same amount of response in early effects (larger therapeutic ratio).

E. Hall Radiobiology for the Radiologist

Why do we fractionate: LQ model Optimization of the therapeutic ratio

- Optimization of fractionation to maximize therapeutic ratio

-Fix target $BED_T = \left(1 + \frac{d_T}{\left(\frac{\alpha}{\beta}\right)_T}\right)$

-Minimize the Normal tissue $BED_{NT} = \left(1 + \frac{d_{NT}}{\left(\frac{\alpha}{\beta}\right)_{NT}}\right)$

if $d_{NT}=d_{TARGET}$ then the well-known result showing

Hypofractionate favorable when $\alpha/\beta_T < \alpha/\beta_{NT}$,

Timmerman 2008, Unkelbach *et al* 2012

To Hypo or to Hyper? Is the sparing factor, stupid!

- But the dose to normal tissue d_{NT} is NOT equal to d_T of target

Sparing factor $\delta = d_{NT} / d_T$

(assume d_{NT} constant in the organ at risk)

then

Hypofractionation is favorable when $\delta . \alpha/\beta_T < \alpha/\beta_{NT}$

If δ<1 as it should hypo may still win even if $\alpha/\beta_T > \alpha/\beta_{NT}$!

Mizuta *et al Int. J. Rad. Onc. Biol. Phys.* 2012

To Hypo or to Hyper? Is the sparing factor, stupid!

- But the dose to normal tissue d_{NT} is NOT constant: in general a DVH reduction method is needed to define δ
- I will loosely define the paring factor $\delta = EUD/D_{NT}$ (Typically <1)

  -EUD stands for “Equivalent Uniform Dose” but not necessarily its original definition by Niemierko

  - EUD can be your favorite DVH reduction method (Lymann model, functional units, etc.)

- Specific definition of δ for serial and parallel structures given in J. Unkelbach *et al* PMB 2012

Hypo Examples for lung and brain SRS, SBRT

- Brain SRS:
  - -small lesions treated with single large doses
  - -main OAR is the normal brain
  - -very rapid dose fall-off due to delivery technique (GammaKnife, SRS Linac)
  - -Low sparing factor δ due to technological advance

- Lung SBRT
  - -Small lesions treated with 3-5 fractions of 10-18Gy
  - -Main OAR is often normal lung
  - -Low δ due to parallel structure of lung function
  - -4DCT, gating, IGRT technology also a factor

To Hypo or to Hyper? Example: prostate cancer

- Prostate cancer game changer: studies showed that α/β_T=1.5-3Gy gives a rationale for hypofractionation from the radiobiological point of view

- IMRT, IGRT, Calypso, space OAR: technologies that reduce the sparing factor make hypofractionation even more favorable

To Hypo or to Hyper? Not just radiobiology

Optimal fractionation schedules depend on radiobiological parameters AND planning techniques AND delivery techniques

To Hypo or to Hyper?
Not that easy: 5 Rs in "RRRRRadiobiology"

But...

So far only 2 Rs: Radiosensitivity ~ α

Repair ~ β, T_{rep}

Still Missing:

Repopulation, Redistribution, Reoxygenation

LQ with Repopulation Simple approach

- Assume exponential growth in the number of clonogens

- Accelerated repopulation during fractionated treatment starts 3-4 weeks after treatment starts

$$N = N_0 e^{\lambda(T-T_k)}$$

$\lambda = \ln(2)/T_{pot}$ repopulation rate

T_{pot} = potential doubling time for the tumor

T_k =kick-off time for accelerated repopulation

T = Overall treatment time ($T>T_k$)

- Biological effect $E = \alpha D\left(1+\frac{d}{\frac{\alpha}{\beta}}\right) - \ln(2)(T-T_k)/T_{pot}$

To Hypo or to Hyper?
How does repopulation affect the calculation

- Therapeutic ratio calculations can be done including a repopulation term

- Qualitatively, adding a repopulation term will favor

  -Hypofractionation (fewer daily fractions)

  -Hyperfractionation but more than 1 fraction per day (CHART, CHARTWEL for lung and head and neck)

LQ Parameter derivation How do we know?

-in vitro data

- Fitting of cell survival curves from Petri-dish experiments
- Data for different dose-rate needed for T_{rep}
- Advantage: can design experiment at will
- Disadvantages:
  - -not in-vivo conditions
  - -different labs may report different data for same cell line

-in vivo animal data

- Fitting iso-effect curves from animal experiments
- Advantage: can design experiment at will
- Disadvantages:
  - -not humans (different biology)

-in vivo data

- Fitting of patient outcome for a given end point..
- Data Stratification needed (risk, dose-levels)
- Advantage: it's the real thing.
- Disadvantages:
  - -Extensive data-sets hard to come by

LQ Parameter derivation In-Vitro Example: Prostate

- Review of 6 prostate cancer cell lines from in-vitro cell survival curves in the literature (ten datasets total).
- LQ model fit with loss function minimization for parameter estimate and boot-strap method to derive 95% confidence intervals
- Results:

α ranged from 0.09 to 0.35Gy^{-1}
$\frac{\alpha}{\beta}$ ranged from 1.09 to 6.29Gy
} all cell lines
T_{rep} ranged from 5.7 to 8.9h

- α and $\frac{\alpha}{\beta}$ results consistent with low $\frac{\alpha}{\beta}$ but T_{rep} longer than in-vivo estimate
- Differences in same cell line from different labs large

D. Carlson *et al* PMB 2004

LQ Parameter derivation
In-Vivo Prostate: Brenner and Hall

1999

Int. J. Radiation Oncology Biol. Phys., Vol. 43, No. 5, pp. 1095–1101, 1999

0360-3016/99/$–see front matter

PII S0360-3016(98)00438-6

BIOLOGY CONTRIBUTION

FRACTIONATION AND PROTRACTION FOR RADIOTHERAPY OF PROSTATE CARCINOMA

DAVID J. BRENNER, D.SC.,* AND ERIC J. HALL, D.SC.*

Center for Radiological Research, Department of Radiation Oncology, Columbia University, New York, NY

Results: Prostatic cancers appear significantly more sensitive to changes in fractionation than most other cancers.

The estimated α/β value is 1.5 Gy [0.8, 2.2]

LQ Parameter derivation
In-Vivo Prostate: Brenner and Hall

- End point
  -FFBF (Freedom from biochemical failure) at 3 years

- Clinical Data (2 reports from the literature)
  -134 patients ^{125}LDR permanent implants based on D_{90} from post-implant dosimetry.
  -5 dose levels

  -237 patients EBRT
    -3 risk levels based on PSA (<10, 10-20 or >10ng/ml)
    -5 dose levels (65-70,70-72.5,72.5-75, 75-77.5,77.5-80Gy)

LQ Parameter derivation Brenner and Hall Assumptions

- Poisson TCP
- LQ model
- G~0 for brachytherapy (based on $T_{rep} << {}^{125}I\ T_{1/2}$) (One less parameter, T_{rep} not involved)
- Prostate repopulation effect negligible
- Uniform LQ parameters across the tumor
- Same RBE for external beam and Brachytherapy
- α and β independent of risk level, only

N_o, initial number of clonogens, determines risk level

Questioning Brenner and Hall Long discussion

- King and Mayo argued a normal distribution of radiosensitivities α with $\sigma_\alpha \rightarrow \alpha/\beta = 4.9Gy$
- Brenner and Hall counter-argued that independent normal distributions for both α and β with $\sigma_{\alpha,}\ \sigma_\beta \rightarrow \alpha/\beta = 2.1Gy$
- Dale and Jones questioned the RBE of LDR prostate implants (much lower energies than external beam)
- Wang *et al* argued repopulation cannot be neglected in ^{125}I brachytherapy because T_{pot}~42 days based on in-vitro reports and dose delivered over several half-lives. Repopulation with T_{pot}~42 days $\rightarrow \alpha/\beta = 3.1Gy$
- …more (too long to go into)

Bottom line
Prostate α/β is low

Commonly Used Prostate Parameter sets

	Brenner and Hall	Wang *et al*
N_o	10-100	10^6-10^7
α(Gy^{-1})	0.036	0.15
α/β(Gy)	1.5	3.1
T_{rep}(min)	-	16
T_{pot}(days)	-	42

Hypofractionation in Prostate Cancer
BIG success of radiobiological modeling

University of Maryland Prostate
current fractionation schemes
Hypofractionation only recently adopted!

	n	d(Gy)	D(Gy)	EQD2($Gy_{1.5}$) Brenner and Hall	EQD2($Gy_{3.1}$) Wang *et al*
Conventional fractionation	44	1.8	79.2	75	76
Conventional fractionation	39	2	78	78	78
Moderate hypofractionation	20	3	60	77	72
Moderate hypo (SIB for high risk)	28	2.5	70	80	77
SBRT (clinical trial)	5	7.5	37.5	96	78
	5	8	40	109	87

EQD2=Equivalent dose in 2Gy
BED/(1+2/(α/β))

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Hypofractionation in Prostate Cancer BIG success of radiobiological modeling

Hypofractionation for prostate cancer is now part of routine clinical practice

- Radiobiological modeling can help guide the decision to hypofractionate
- Randomized Clinical Trials are needed to determine how much and for what patients
- Any parameter derivation has to be thoroughly tested clinically

University of Maryland
School of Medicine

So far 3 Rs
Oxygen Effect and Reoxygenation

- Oxygen effect is well known:

-Early in-vitro experiments of mammalian cells irradiated in the presence and absence oxygen showed significantly more radiosensitivity for oxygenated cells.

-OER=Oxygen Enhancement Ratio is the ratio of hypoxic to aerated doses needed to achieve the same biological effect

-For X-rays and γ rays at high doses, OER~2.5-3 (maybe lower for lower doses)

LQ with Reoxygenation How to do it? Two-compartments

- Oxygen Levels and tumor radiosensitivity is non-uniform across the tumor.
- Many radiobiological modeling studies proposed variations of the LQ model to include these effects.
- Two-compartment models (one aerobic and one hypoxic) have often been used due to its simplicity and the believe that they capture the essence of the problem.
- Some kinetic models consider cells moving from the hypoxic compartment to the aerobic compartment to include the reoxygenation effect

LQ with Reoxygenation
Simple approach for fractionated RT

- Define two compartments with different radiosensitivities:

- $S(d)_A$ for aerobic compartment with fraction f_A of N_o

- $S(d)_H$ for hypoxic compartment with fraction f_H=1-f_A of N_o

-S(d) given by LQ model with

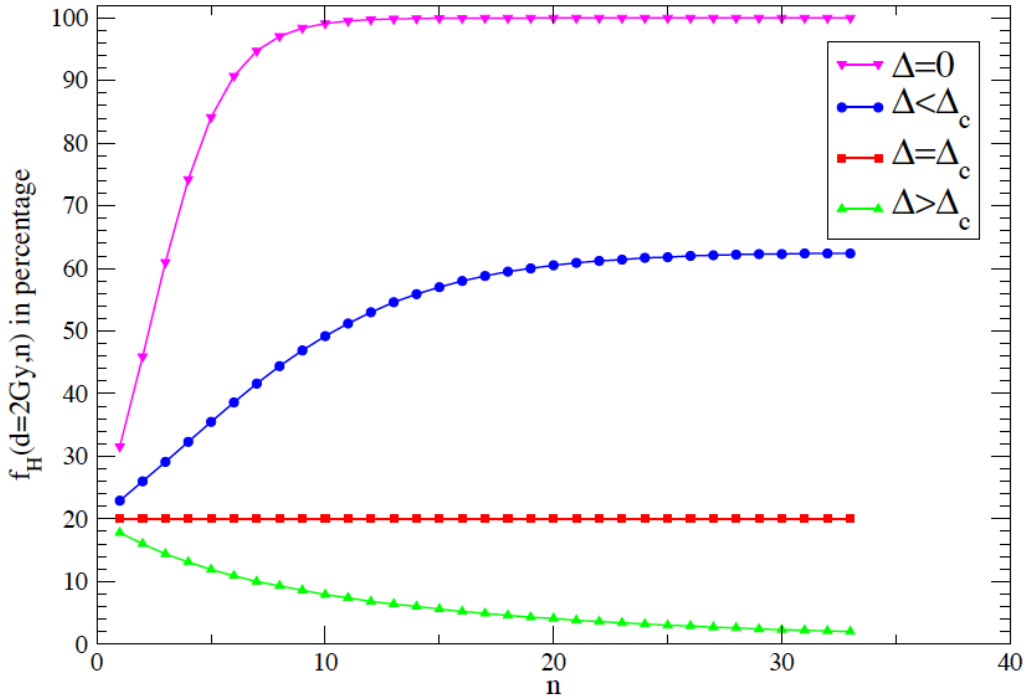
$\alpha_A=\alpha_H \cdot OER$ and $\beta_A=\beta_H \cdot OER^2$ and $(\alpha/\beta)_A=(\alpha/\beta)_H$/OER.

- fraction Δ of the remaining hypoxic cells after each radiation treatment fraction of dose *d*, moves from the hypoxic compartment to the aerobic compartment

M. Guerrero and D. Carlson Med. Phys 2017

LQ with Reoxygenation
Hypoxic fraction vs number of fractions
)

- Critical Value of the reoxygenation parameter Δ_C



$$\Delta_C = \frac{\frac{f_A}{f_H}\left(1-\frac{S(d)_A}{S(d)_H}\right)}{1+\frac{f_A}{f_H}}$$

- Δ_C Determines the behavior of the hypoxic fraction vs n

M. Guerrero and D. Carlson Med. Phys 2017

LQ with Reoxygenation
What about optimization of fractionation?

-Not aware of such calculation

-Qualitatively, if reoxygenation was independent of the interval between fractions and dose per fraction, it should favor hyperfractionation

-However, the temporal and dose dependence of the reoxygenation process for fractionated RT is not known

-A lot more work to do!

LQ with Redistribution? We are missing an R!

- Currently I am not aware of a practical model to include redistribution in the LQ model
- In principle, two-compartment models can potentially describe cells in different parts of the cycle with different radiosensitivity
- However, parameters appropriate for cell cycle effects would have to be developed and used for such model to be meaningful

Biologically Adaptive Radiation Therapy (BART)  *How can we do it?*

- Use Molecular Imaging to "measure" individual patients' radiobiological parameters!
- Dose-Painting: assigning higher dose levels to areas of the tumor at "higher risk" based on the marker:

-FDG uptake in PET images is considered a surrogate for tumor burden (clonogenic cell number, N_o)

-^{18}F-fluorothymidine (FLT-PET) uptake is believed to be a surrogate for tumor growth (Repopulation)

-^{18}F-misonizadole (MISO) and several other tracers can detect low oxygen levels in tumor (hypoxia, reox)

BART Example
Head and Neck Hypoxia studies

- Identify hypoxic regions in tumor based on PET with hypoxia tracer.
- Deliver a higher dose to the hypoxic regions identified
- “Proof of concept” planning studies suggest 15-20% increase in dose needed to overcome hypoxia
- Several ongoing clinical trials. No definite results yet.

BART Example
Head and Neck Hypoxia studies

- A Phase II study with dose painting compared 70Gy vs. 77Gy in 35 fractions (25 patients, HN SCC) was shown safe and potentially effective (Welz *et al* 2017)

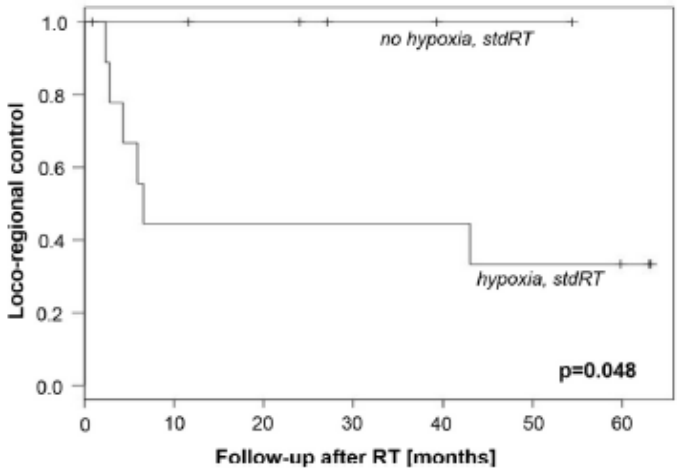


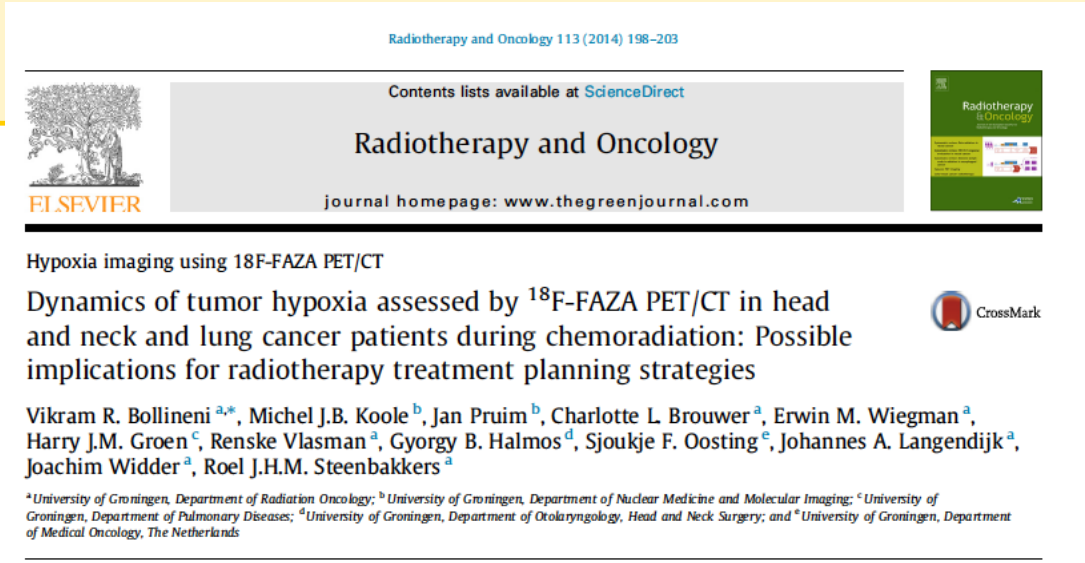
Fig. 2. Kaplan–Meier plot of loco-regional control for patients with non-hypoxic tumours compared to the group of patients presenting with hypoxic tumours treated with stdRT.

stdRT=standard RT

-Hypoxic patients receiving dose escalation not shown but had 70% locoregional control

-Caution: small number of patients (20 hypoxic, 10 dose escalated, 5 non-hypoxic)

Longitudinal study



Radiotherapy and Oncology 113 (2014) 198–203

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journal homepage: www.thegreenjournal.com

Hypoxia imaging using 18F-FAZA PET/CT

Dynamics of tumor hypoxia assessed by ^{18}F-FAZA PET/CT in head and neck and lung cancer patients during chemoradiation: Possible implications for radiotherapy treatment planning strategies

Vikram R. Bollineni [a,*], Michel J.B. Koole [b], Jan Pruim [b], Charlotte L. Brouwer [a], Erwin M. Wiegman [a], Harry J.M. Groen [c], Renske Vlasman [a], Gyorgy B. Halmos [d], Sjoukje F. Oosting [e], Johannes A. Langendijk [a], Joachim Widder [a], Roel J.H.M. Steenbakkers [a]

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-^{18}F-FAZA PET at 0, 1, 2, and 4 weeks during treatment: follow changes in hypoxic volumes during treatment

-Hypoxic volumes defined as volumes with uptake more than 1.4 relative to background

-Clinical studies also use a two-compartment approach!

6 Patient Result

hypoxic volume and uptake value changes

Patient	Baseline		1st week CHRT		2nd week CHRT		4th week CHRT	
	FAZA-T/B	FHV (%)	FAZAT/B	FHV (%)	FAZA-T/B	FHV (%)	FAZA-T/B	FHV (%)
1	1.7	5	1.5	1	1.7	5	1.4	0
2	2.0	47	1.9	28	1.5	5	1.2	0
3	1.7	39	1.6	33	1.5	32	–	–
4	3.0	85	–	–	1.8	24	1.4	5
5	2.1	37	–	–	1.9	20	1.5	1.7
6	1.8	18	1.6	1	–	–	–	–

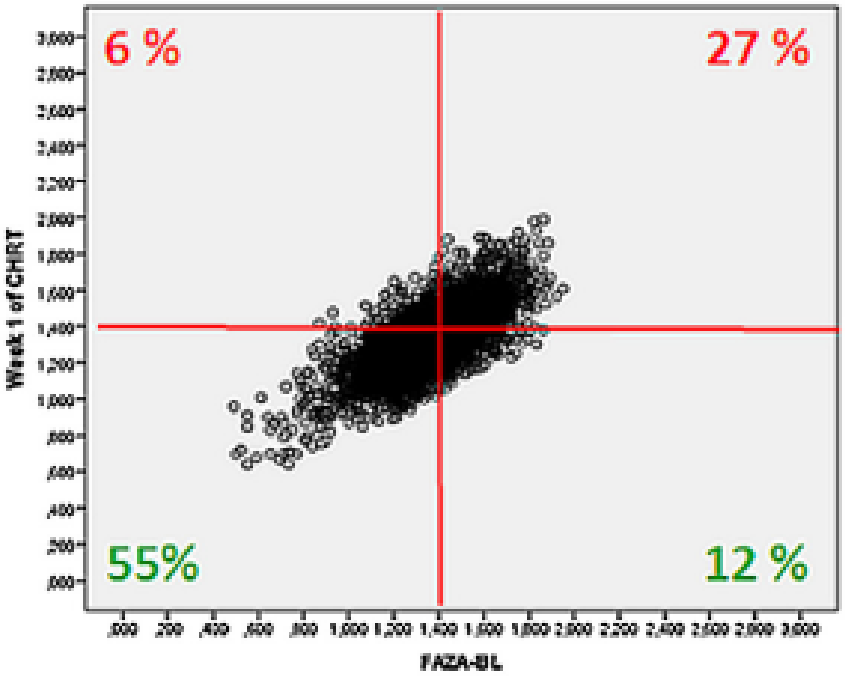
-FAZA T/B is the tumor to background uptake ratio (could potentially be a surrogate for OER?)

-FHV is the fractional hypoxic volume in percentage(defined as volume with uptake larger than 1.4)

-HN patients saw stable or decreased hypoxia as treatment advanced (not always the case)

Bollineni *et al* 2014

Hypoxia can be a dynamic process
Scattered plots of hypoxic voxels



-Initial aerobic voxels can become hypoxic and vice-versa

-This may show a drawback for dose-painting based on initial scan

Bollineni *et al* 2014

More examples of BART
Other anatomical sites

- Boost dose for Intra-prostatic lesions based on functional MRI
- PET-based molecular studies of lung tumors
- Conventional MRI volume reduction adaptation (big deal these days thanks to MR-linacs)
- …many more

Models of Radiation Response
What is to come

-Particle therapy and RBE uncertainty at far end of Bragg peak (Active area, still a way to go).

-Machine learning + radiobiological modeling (How to do this? Should we do this?)

-New technologies: e.g. FLASH (Very active area, in its infancy)

-Others: Immunotherapy? Nanoparticles?....

References

1-Munro and Gilbert (1961) Br. J Radio **34** 246-51.
2-Bentzen (2009) "Dose-response relationships in radiotherapy" in "Basic Clinical Radiobiology" edited by M. Joiner and A. van der Kogel
3-Sachs R K, Hahnfeldt P J, and Brenner D A (1997) Int. J. Radiat. Biol. **72** 351–74
4-E. Hall "Radiobiology for the Radiologist (any edition).
5-Timmerman R D (2008) Semin. Radiat. Oncol. **18** 215–22
6- Mizuta M, *et al*(2012) Int. J. Radiat.Oncol. Biol. Phys. **84** 829–33
7- Jan Unkelbach, David Craft, Ehsan Salari *et al* (2013) Phys. Med. Biol. 58159–167.
8- David J Carlson *et a*l. (2004) Phys. Med. Biol. **49** 4477–4491.
9- Brenner DJ, Hall EJ. Int J Radiat Oncol Biol Phys1999;43:1095–1101.
10- King CR, Mayo CS (2000) 47 536–538.
11- Brenner DJ, Hall EJ. (2000) Int J Radiat Oncol Biol Phys 2000; **47**:538–539.
12-Wang JZ *et al* (2003). Int J Radiat Oncol Biol Phys; **55**:194–203.
13- M. Guerrero, D. Carlson (2017) Medical Physics Journal Vol: **44** 2002–2010.
14-Welz *et al.* (2017) Radiotherapy and Oncology **124** 526–532
15-V. Bollineni *et al* (2014) Radiotherapy and Oncology **113** 198–203.

Thank you!

Questions?