Comparative Radiobiology of Fluoroscopically-Guided Interventions (FGI) and External Beam Radiation Therapy (EBRT)

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Location: TU-E-221CD

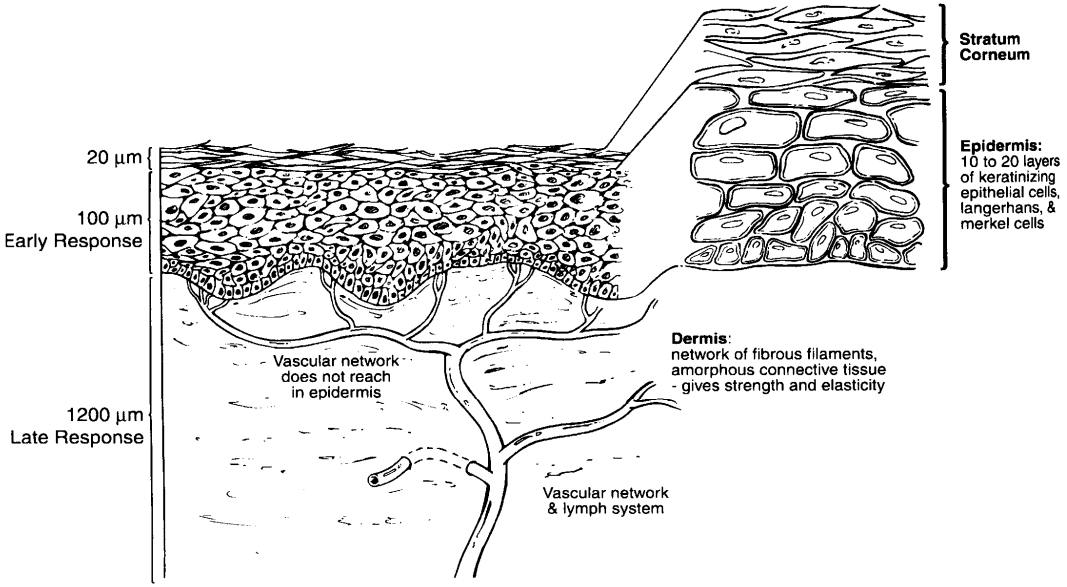
Learning Objectives

- **Review basic radiobiological principles (**R's of Radiation Biology**) and related biological metrics, such as EQD2 (***equivalent dose in 2 Gy fractions***)**
- **Illustrate the use of the EQD2 concept to assess and compare FGI and EBRT with regards to**
  - Dose per procedure ("fraction size" in EBRT) and accumulated total dose
  - Intra- and inter-procedure dose rate effects
  - Relative biological effectiveness (RBE) of kV x-rays relative to MV x-rays
  - Recovery and self-renewal of normal tissue with a focus on comparative assessments of the risks from FGI procedures and EBRT

Disclaimer

- Passionate about radiation biology and personalized treatment guidance to improve outcomes and reduce toxicity
- Otherwise nothing to disclose

Radiation Damage and Recovery of Skin



Some relevant biological considerations

- Induction and repair of DNA damage to individual cells
- Cell division and migration within the epidermis and dermis
- Vascular damage and recovery
- Relative biological effectiveness (RBE) of kV and MV x-rays
- Volume of irradiated tissue

- Epidermis (outer layer): active cell proliferation → *early* radiation reactions

- Dermis (deeper layer): connective tissue (some cell division) → *late* radiation reactions

R's of Radiation Biology

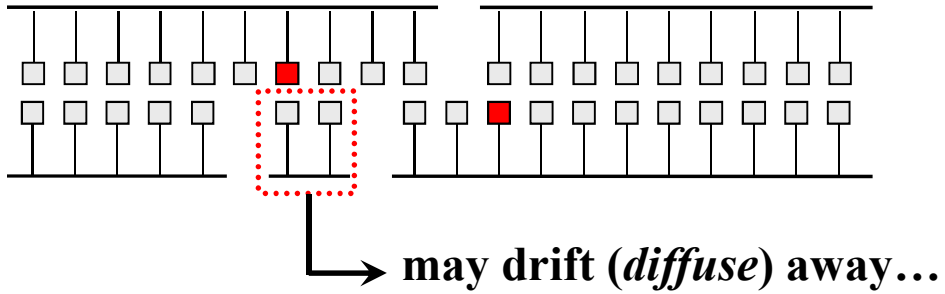
- **R**epair (*biochemical repair of DNA damage*) → dose and dose rate effects
- **R**elative Biological Effectiveness (RBE) → kV x-ray RBE > MV x-ray
- **R**ecovery and self-**R**enewal of normal tissues → when can we safely treat again?
- **R**edistribution of cells in the cell cycle
- **R**e-oxygenation of tumor cells
- **R**epopulation of tumors cells
- **R**eimbursement for patient care

Initial Molecular Endpoints

(*1*) *Direct* ionization of membranes, proteins, RNA, DNA, …
(*2*) *Hydroxyl radicals* (·OH) and other reactive oxygen species (ROS) indirectly damage the same

DNA double strand break (DSB) widely (*and still*) considered most critical molecular insult

Break-ends formed by ionizing radiation are chemically reactive ("sticky")

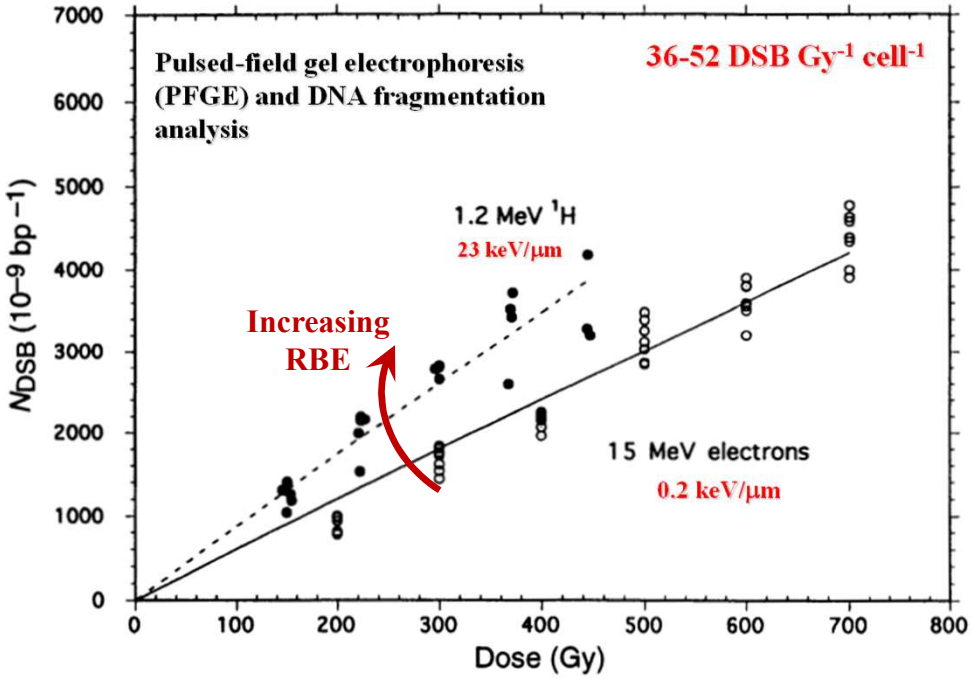


DSB induction ∝ dose, no dose rate effect, contributes to RBE

∝ up to doses of hundreds of Gy
Damage complete within μs to ms

<u>No</u> dose rate effect up to thousands of Gy s^{-1}

RBE for DSB induction increases with increasing linear energy transfer (LET)



Frankenberg D, Brede HJ, Schrewe UJ, Steinmetz C, Frankenberg-Schwager M, Kasten G, Pralle E. Induction of DNA double-strand breaks by 1H and 4He ions in primary human skin fibroblasts in the LET range of 8 to 124 keV/microm. *Radiat Res.* 151(5), 540-549 (1999).

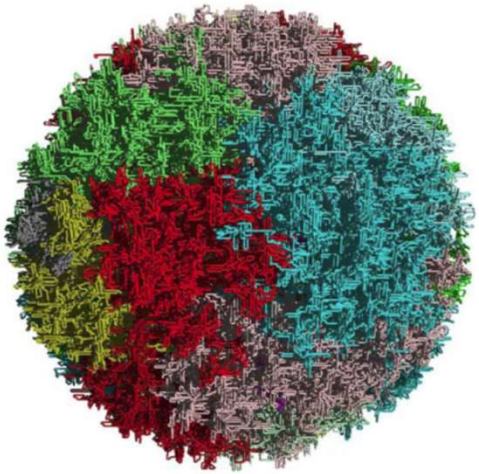
DSB and Chromosomes

Each chromosome in a human cell is tens or hundreds of millions of bp in length (*hundreds of μm in length*)

The 46 very long DNA molecules (*chromosomes*) are packed into a region on the order of 5 μm in diameter

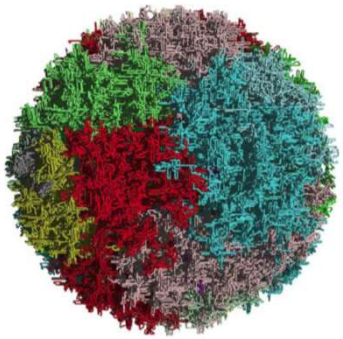
DSB

Pair of free break-ends



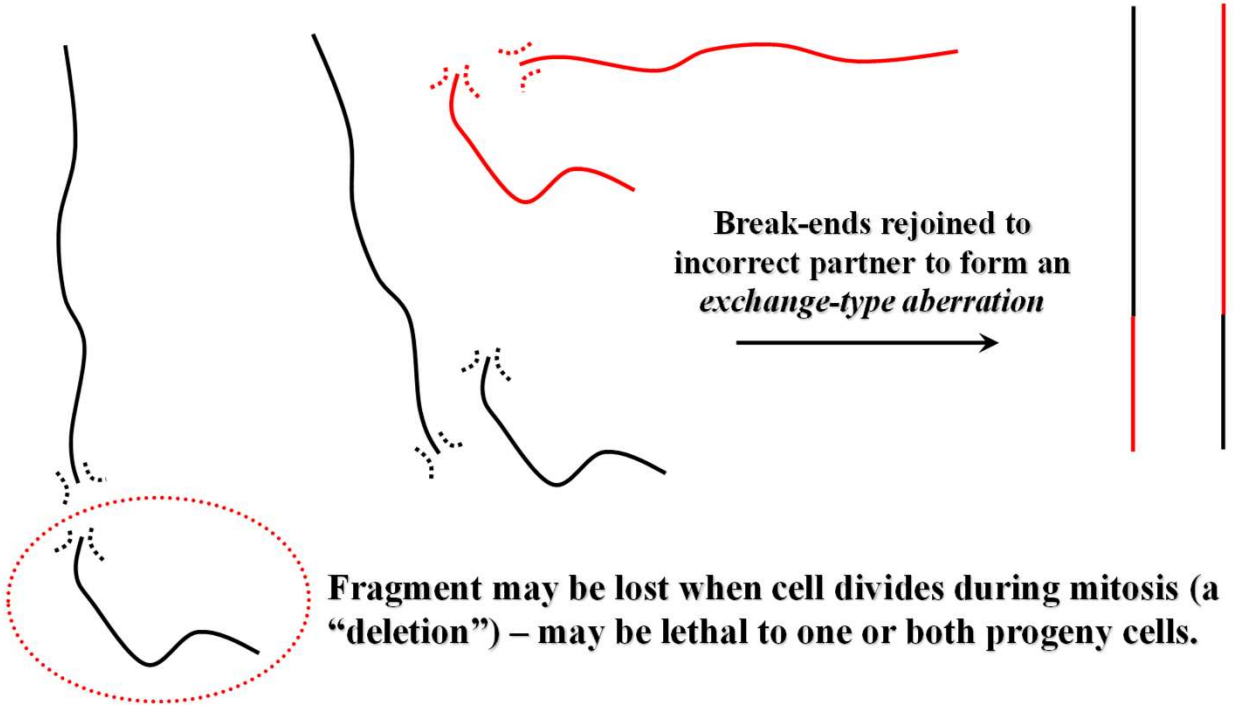
Chromosomes in a human lymphocyte (Friedland *et al.* REB, 47, 49-61, 2008)

Chromosome Aberrations



Chromosomes in a human lymphocyte
(Friedland *et al.* REB, 47, 49-61, 2008)

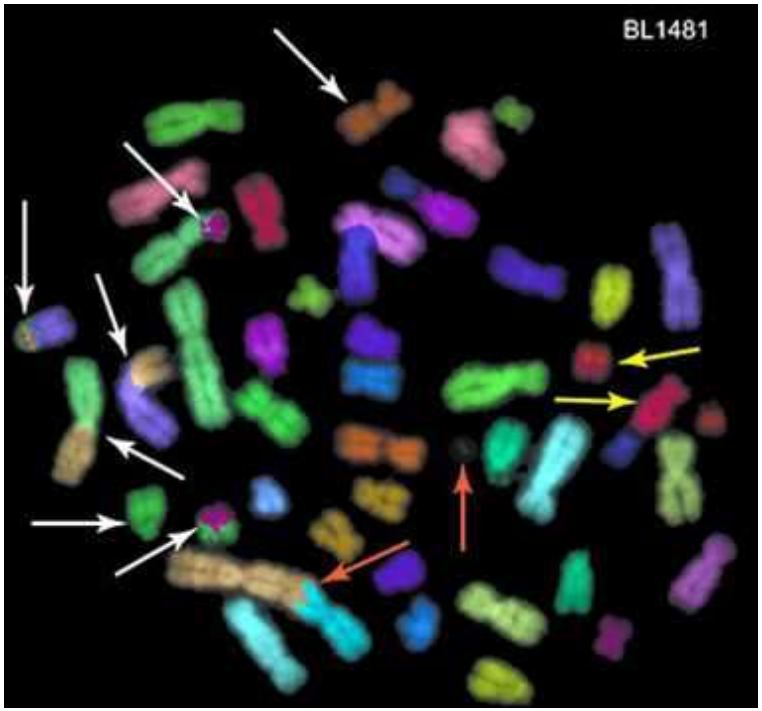
Large-scale (*tens of thousands or millions of bp*) rearrangements, deletion or duplication of the DNA forming a chromosome



Fragment may be lost when cell divides during mitosis (a "deletion") – may be lethal to one or both progeny cells.

mFISH image of chromosome aberrations

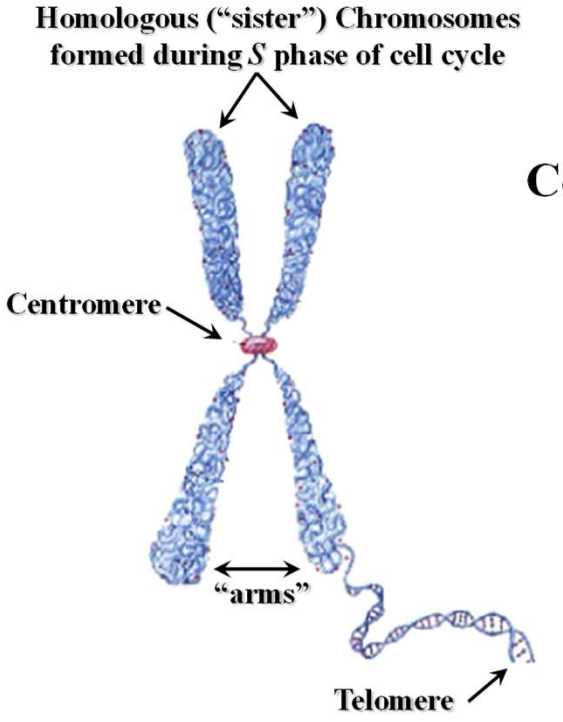
- White arrows
  - Complex exchange-type aberrations
  - Chromosomes 1, 2, 3, 9, 11, 20
- Red arrows
  - Dicentric
  - Chromosome 1 and X
- Yellow arrows
  - Translocation
  - Chromosome 12 and 21

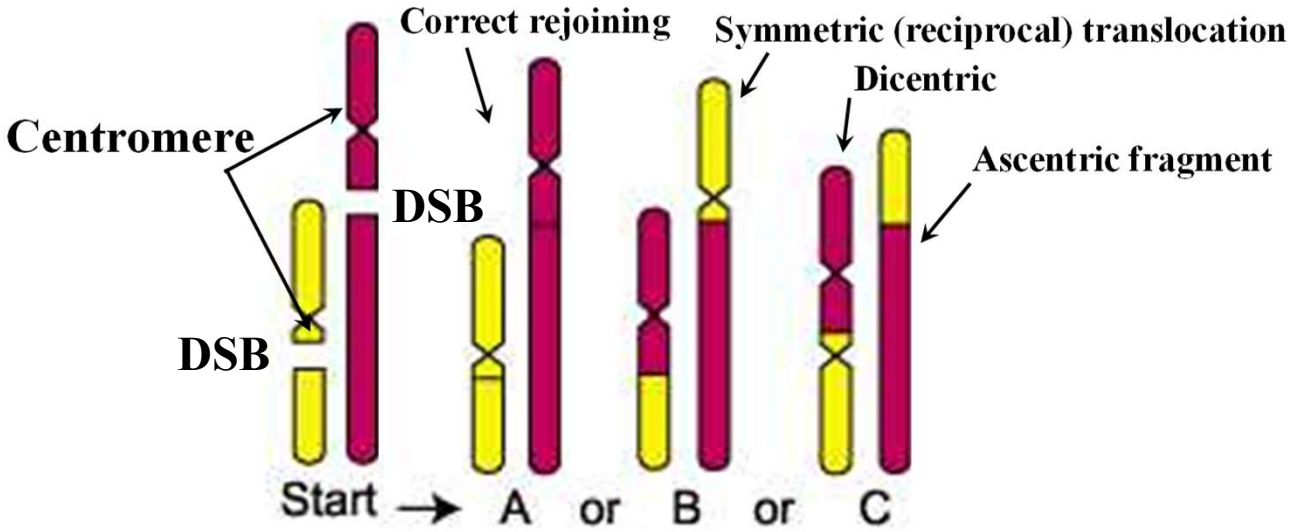


mFISH: multi-color fluorescence in situ hybridization

R.K. Sachs and D.J. Brenner, Chromosome Aberrations Produced by Ionizing Radiation: Quantitative Studies
http://web.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowTOC&rid=mono_002.TOC&depth=10

Lethal and Non-lethal Chromosome Aberrations





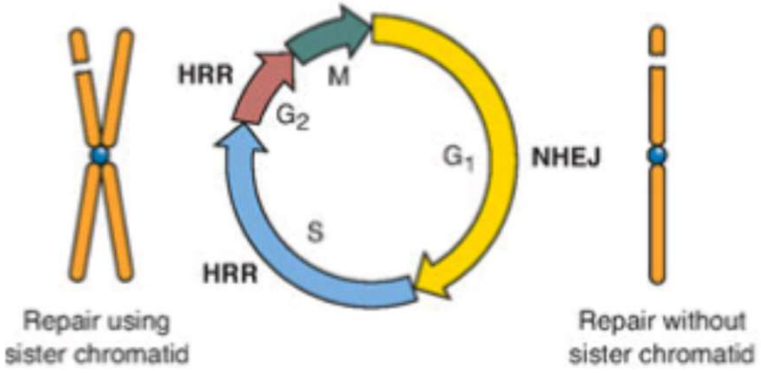
A = point mutation (*mostly non-lethal*)

B = non-lethal, highly mutagenic (*stochastic effects*)

C= reproductive lethality (*cell killing, clinical endpoints*)

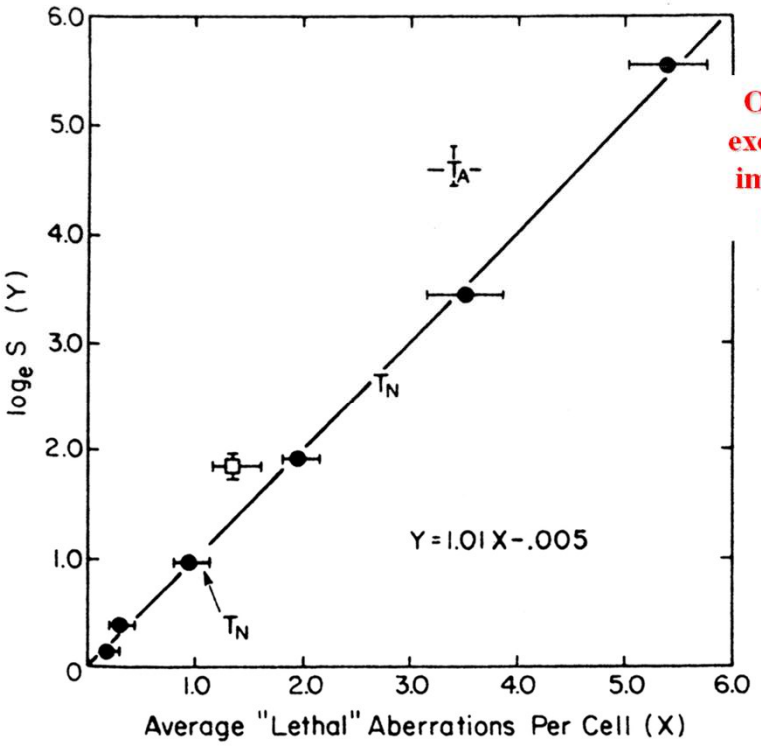
Biochemical *R*epair – DSB → Chromosome Aberrations

- **Two major DSB repair pathways are non-homologous end joining (NHEJ) and Homologous Recombination (HR)**
  - In human cells, NHEJ active in all phases of cell cycle (G1, S, G2 and M). HR is highly suppressed in mammalian cells, except in mid-late S phase and early G2
- **Over 97% of initial DSB produced by low and high linear energy transfer (LET) radiations are rejoined (*correctly or incorrectly*)**



It is the biochemical processing of initial DSB into chromosome aberrations that gives rise to *dose rate effects*

Chromosome Aberrations and Cell Survival



One to one correlation between lethal exchanges (dicentrics and centric rings) implies this form of damage is a major reason cells are killed by radiation

AC 1522 normal human fibroblasts irradiated by x-rays

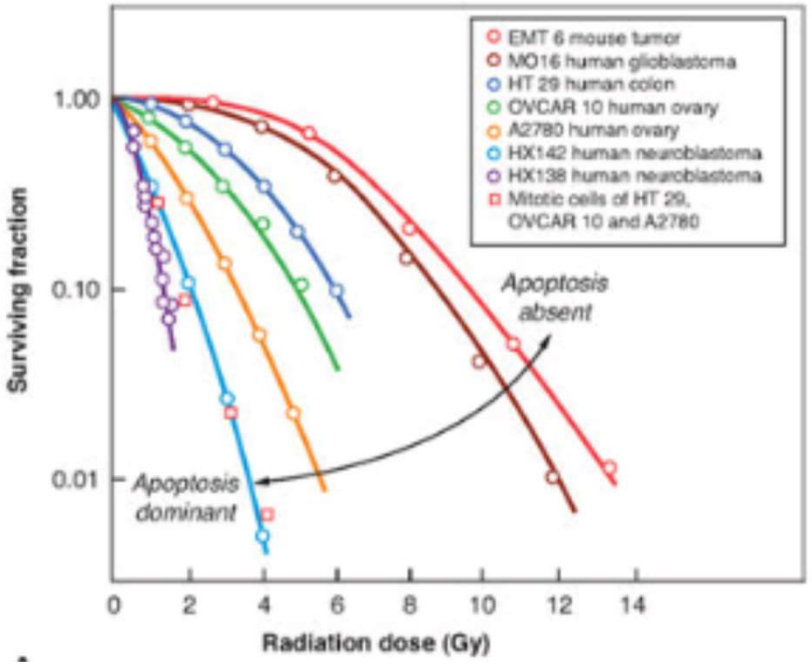
Dose rate effects **are included through Lea-Catchside dose protraction factor, *G***

$$S(D) \cong \exp\left[-Y(D)\right]$$

$$= \exp\left[-\alpha D - \beta G D^2\right]$$

Source: Cornforth and Bedford, *Rad. Res.*, 111, p 385-405 (1987). See also Figure 3.4 in Hall (p. 37)

Apoptosis and Radiation Sensitivity



Mitotic Death
(*chromosome aberrations*)

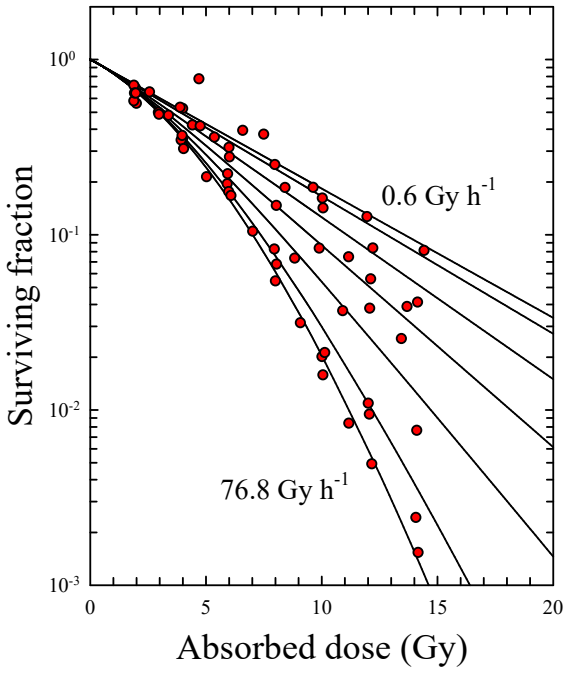
$$S(D) = \exp\left\{-(\alpha_A + \alpha_M)D - \beta_M G D^2\right\}$$

apoptosis

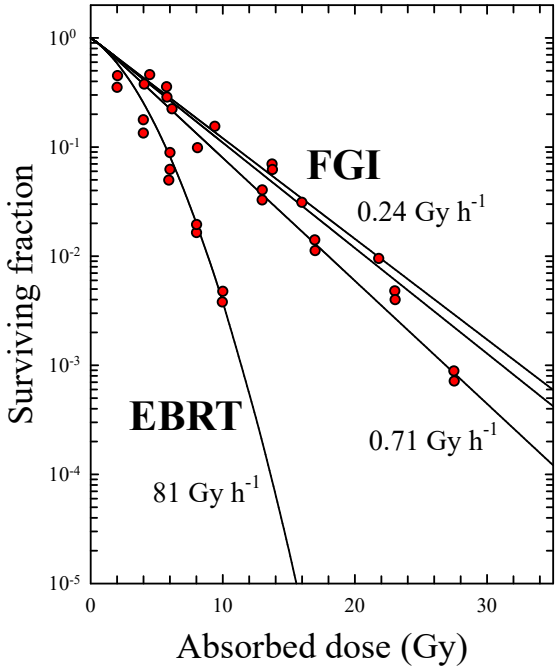
Dose rate effects are included through *G* (dose protraction factor)

Figure 3.8 in Hall and Giaccia, Radiobiology for the Radiologist 7th Ed. Lippincott, Williams and Wilkins (2012)

Effect of Dose Rate on Cell Survival



RT112 human bladder carcinoma



AG1522 normal human fibroblast

External beam radiation therapy (EBRT) ~ 60 Gy h^{-1}

Fluoroscopically-Guided Interventions (FGI)

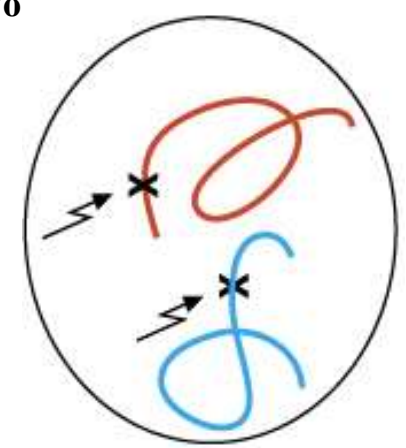
Dose (Gy)	Procedure Duration (h)	Dose Rate (Gy h^{-1})
2.00	2.00	1.00
4.00	2.00	2.00
6.00	4.00	1.50
8.00	8.00	1.00
12.00	6.00	2.00
16.00	12.00	1.33

Measured data from Ruiz de Almodovar JM, Bush C, Peacock JH, Steel GG, Whitaker SJ, McMillan TJ. *Radiat. Res.* 138, S93-S96 (1994) and Hall EJ, Marchese MJ, Astor MB, and Morse T. *Int. J. Radiat. Onc. Biol. Phys.* 12, 655-659 (1986).

Conceptual basis for dose rate effects

Aberrations are formed through the interaction of pairs of DSB formed by the same or two different track (*breakage and reunion theory*).

- **Pairs of DSB created by same particle track ∝ dose and create at same instant in time**
- **Pairs of DSB created by different tracks ∝ square of dose and may be created at time times**



A *pair* of DSB can only interact to form an exchange if they are present in the cell at the same time. If one DSB is rejoined before a second is created, they cannot interact to form an exchange

- **DSB must be in close spatial *and temporal* proximity with each other to interact in pairwise fashion for form lethal and non-lethal chromosome exchanges.**

One-track mechanism
(Interacting DSB **created at same instant in time**

Two-track mechanism
(DSB may or may not be in "close temporal proximity")

Yield of chromosome exchanges

$$Y = \alpha D + \beta G D^2$$

- **Lea-Catchside dose protraction factor**

Modeling Dose Rate Effects in the Linear Quadratic (LQ) Model

$$S = \exp\left(-\alpha D - \beta G D^2\right)$$

$x \equiv \Delta t \ln 2 / \tau \longrightarrow$ **Half-time for sub-lethal DSB repair**

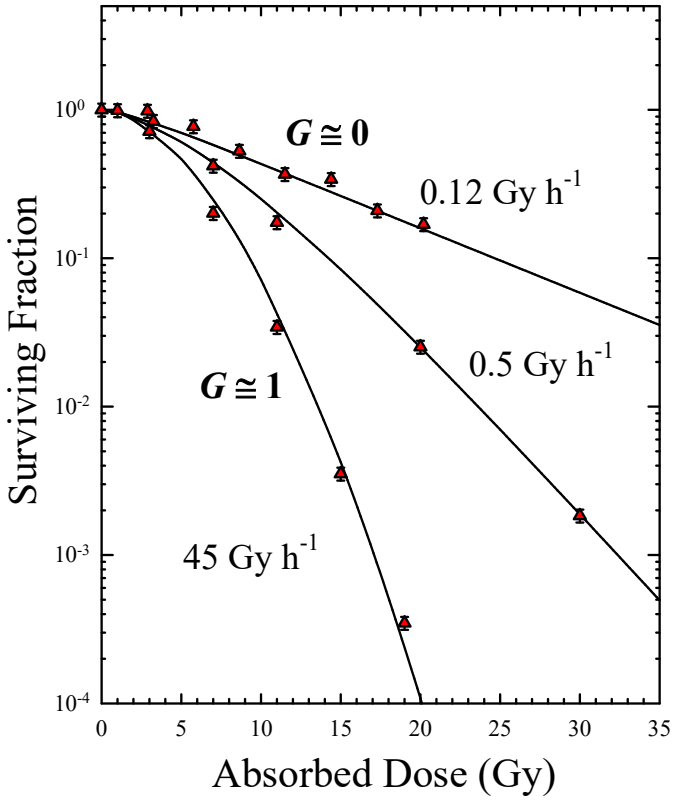
$$\Delta t = D / \dot{D}$$

dose

dose rate

$$G = \frac{2}{x^2}\left(e^{-x} + x - 1\right)$$

G **decreases from unity towards zero as dT becomes large**



α and β independent of dose rate

RBE for DSB induction and cell survival

For kV and MV x-rays, RBE for DSB induction (RBE_{DSB}) accurately determines the RBE for cell survival (Streitmatter *et al.* 2017)

$$S = \exp\left(-\alpha \cdot D - \beta G \cdot D^2\right)$$

RBE_{DSB} = 1.0 (*all photons and electrons*)

$$= \exp\left(-\alpha \cdot RWD - \beta G \cdot RWD^2\right)$$

where $RWD \equiv RBE_{DSB} \cdot D$

Low energy electrons and kV x-rays (< 160 kV) create 10 to 40% more DSB Gy^{-1} than ^{60}Co γ-rays or MV x-rays.

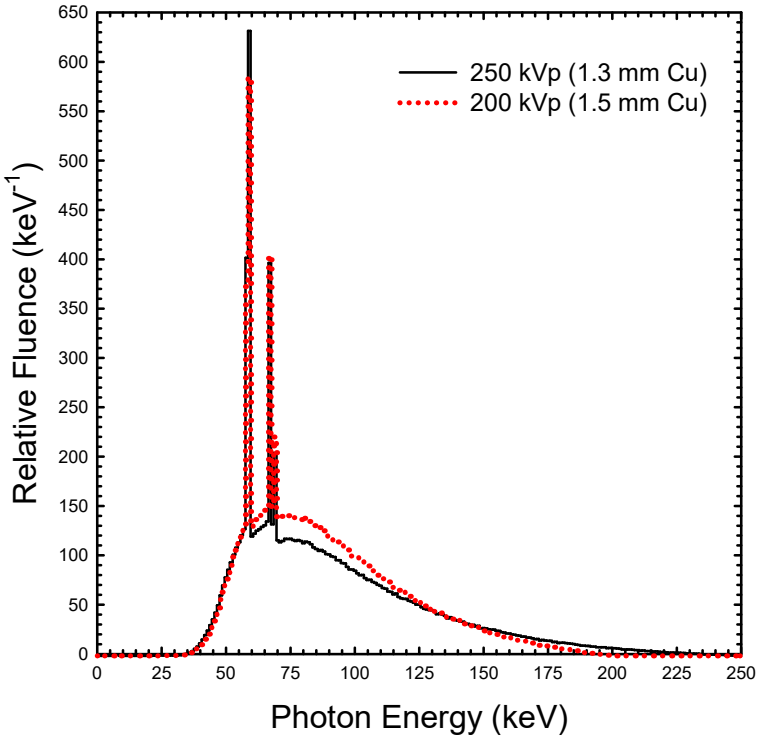
Cell killing and mutagenesis tends to increases as number of DSB increases.

RBE_{DSB} ~ 1.2 to 1.3 (*soft kV x-rays*) to about 1.1 for heavily filtered (*hard*) kV x-rays (Stewart *et al.* 2015)

Streitmatter SW, Stewart RD, Jenkins PA, Jevremovic T. DNA double strand break (DSB) induction and cell survival in iodine-enhanced computed tomography (CT). Phys Med Biol. 2017 Jul 13;62(15):6164-6184.

Stewart RD, Streitmatter SW, Argento DC, Kirkby C, Goorley JT, Moffitt G, Jevremovic T, Sandison GA. Rapid MCNP simulation of DNA double strand break (DSB) relative biological effectiveness (RBE) for photons, neutrons, and light ions. Phys Med Biol. 2015 Nov 7;60(21):8249-74.

RBE for x-ray RBE_{DSB} varies with kV setting and filtration



kV setting alters the relative number of low-energy (*high RBE*) and high-energy (*RBE ~ 1.00*) x-rays

Filtration knocks down number of low-energy (*high RBE*) photons ("hardens beam")

Composition of anode (Rh, Mo, W**) does not have much impact on RBE but it is important from an imaging and dosimetric perespective**

Stewart RD, Streitmatter SW, Argento DC, Kirkby C, Goorley JT, Moffitt G, Jevremovic T, Sandison GA. Rapid MCNP simulation of DNA double strand break (DSB) relative biological effectiveness (RBE) for photons, neutrons, and light ions. Phys Med Biol. 2015 Nov 7;60(21):8249-74.

Equivalent Dose in 2 Gy fractions (EQD2)

- In EBRT, long history of using "conventional fractionation" (~ 2 Gy per day up to ~ 60 Gy) for the treatment of cancer (curative intent)
- EBRT uses high dose rates for individual fractions (~ 60 Gy h^{-1}) but the use of daily fractionation tends to mimic lower rate rates (allows for tissue repair)
- Over last 10-20 years, major trend in radiation oncology towards hypofractionation (large dose per fraction, smaller total doses)
- EQD2 concept is a useful ***biological metric*** that can be used to compare alternate EBRT treatments in an apples-to-apples way
- Also a useful metric to compare treatment toxicity from EBRT **and FGI procedures**, as long as we account for RBE and intra- and inter- procedure dose rate effects and have good dosimetry.

EQD2 Formula in EBRT

As usually seen in radiation oncology literature, EQD2 given as

$$-\ln S/\alpha = D\left(1+\frac{d}{\alpha/\beta}\right) = EQD2\left(1+\frac{2\ \text{Gy}}{\alpha/\beta}\right)$$

D **= total dose (Gy)**
n **= number of fractions**
d **=** ***D*****/*****n*** **(*fraction size*)**

$$\therefore EQD2 = D\frac{\left(1+\frac{D/n}{\alpha/\beta}\right)}{\left(1+\frac{2\ \text{Gy}}{\alpha/\beta}\right)}$$

This formula does not account for differences in effective dose rates used in FGI procedures (< 1 Gy h^{-1}) and EBRT (~ 60 Gy h^{-1}) nor RBE effects.

Generalized EQD2 Formula for FGI Procedures

$$EQD2 = RWD \cdot \frac{\left(1 + \frac{RWD \cdot G_{FGI}}{\alpha / \beta}\right)}{\left(1 + \frac{2\ \text{Gy}}{\alpha / \beta}\right)}$$

RWD = RBE_{DSB} × (FBI procedure dose)

RBE_{DSB} ~ 1.2 to 1.3 (*soft kV x-rays*) to about 1.1 for heavily filtered (*hard*) kV x-rays (Stewart *et al.* 2015)

Formula converts total dose from a FGI procedure delivered at low effective dose rates into a biologically equivalent EBRT dose delivered in 2 Gy daily fractions at high dose rate.

Stewart RD, Streitmatter SW, Argento DC, Kirkby C, Goorley JT, Moffitt G, Jevremovic T, Sandison GA. Rapid MCNP simulation of DNA double strand break (DSB) relative biological effectiveness (RBE) for photons, neutrons, and light ions. Phys Med Biol. 2015 Nov 7;60(21):8249-74.

Dose Protraction Factor for a Single FBI Procedure, G_{FGI}

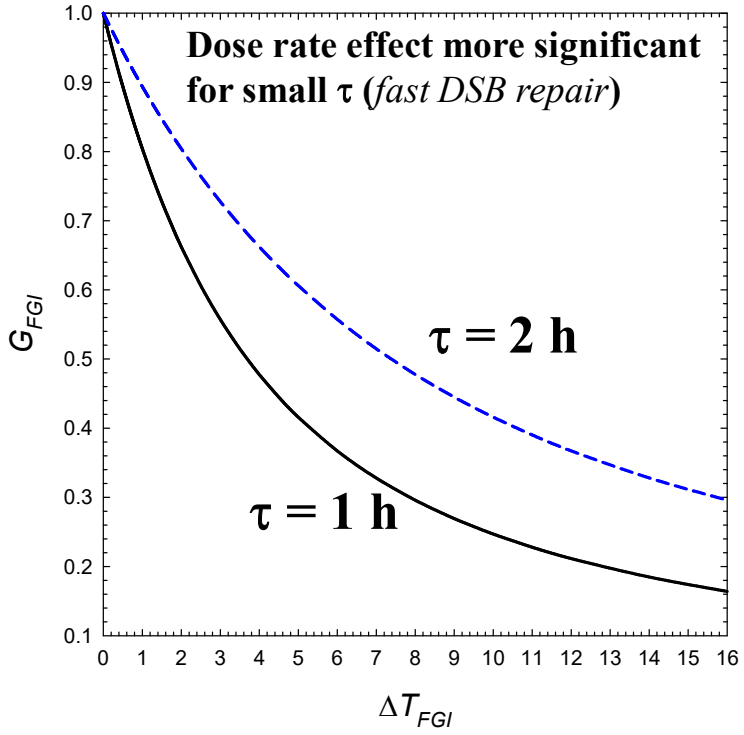
For a single FGI procedure delivered over time interval ΔT_{FGI}, the dose protraction factor is well approximated by

$$x \equiv \Delta T_{FGI} \cdot \ln 2 / \tau$$

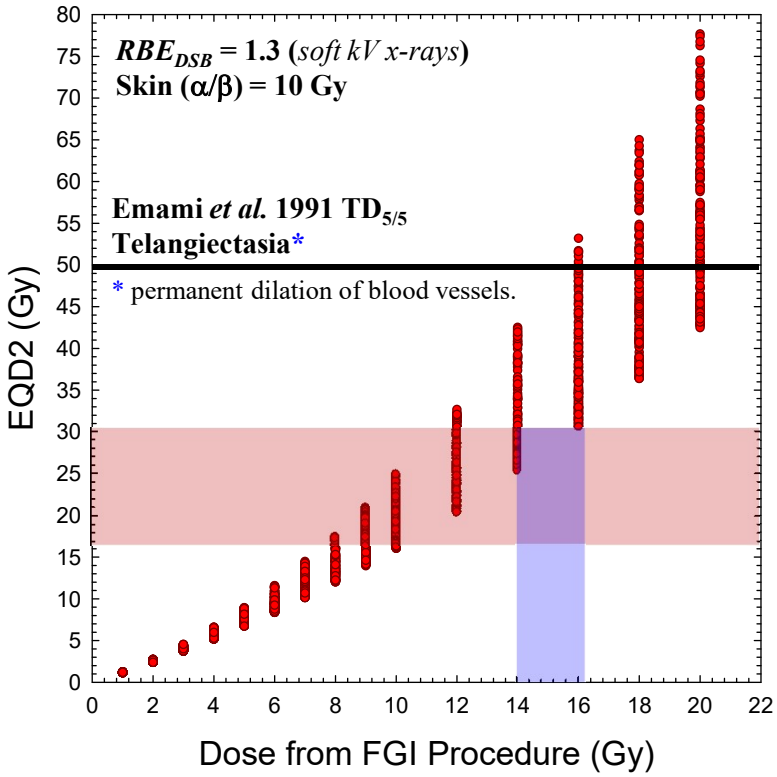
Half-time for sub-lethal DSB repair (~ 1-2 h)

$$G_{FBI} = \frac{2}{x^2}\left(e^{-x} + x - 1\right)$$

Changes in *instantaneous dose rate* over time scales of seconds to 5-10 minutes irrelevant because τ ~ 1-2 h. It is the average dose rate that determines the extent of biologically relevant repair.



EQD2 as a function of FGI procedural dose and duration



Vertical range of EQD2 values reflect effect of procedure duration (randomly sampled value of ΔT_{FGI} from 0 to 12 h**)**

Not uncommon to see mild to moderate erythema (*skin redness***) after 2-3 weeks of conventional EBRT with MV x-rays (**EQD2 ~ 15 to 30 Gy**). Usually clears up within 2-3 weeks after treatment. Easily managed and not treatment limiting in longer term.**

Rough Estimate of EQD2 for Various Skin Reactions

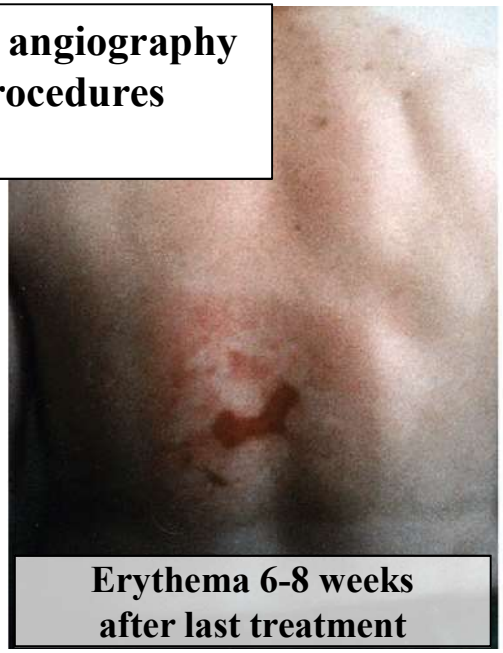
EQD2	
< 10 Gy	No visible reaction
< 15 Gy	Faint erythema
< 30 Gy	Erythema increasing to marked erythema (skin recovers after 2-3 weeks)
~ 50 Gy	Telangiectasia = permanent dilation of blood vessel ($TD_{5/5}$ Emami *et al.* 1991)
~ 55-70 Gy	Moist desquamation followed by potential for necrosis (*dead tissue*), ulceration and scarring in longer term ($TD_{5/5}$ Emami *et al.* 1991)

Keep in mind FGI dose to → EQD2 depends on ΔT_{FGI}, τ, (α/β), and RBE_{DSB}

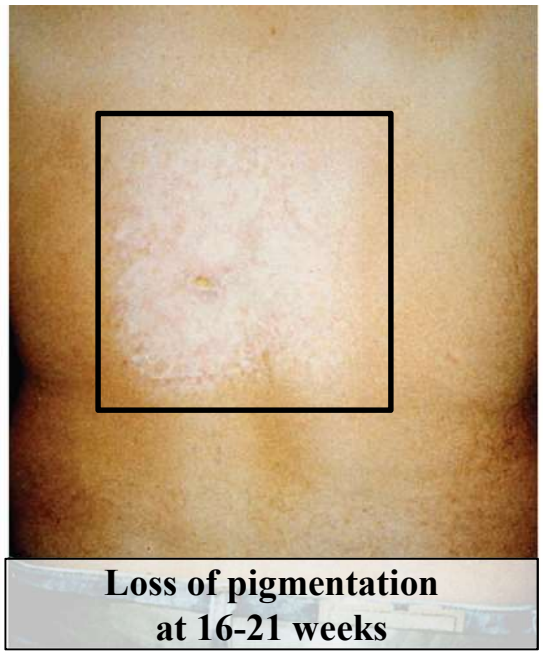
What about multiple FGI Procedures?

Multiple coronary angiography and angioplasty procedures (Balter *et al.* 2010)

EQD2?

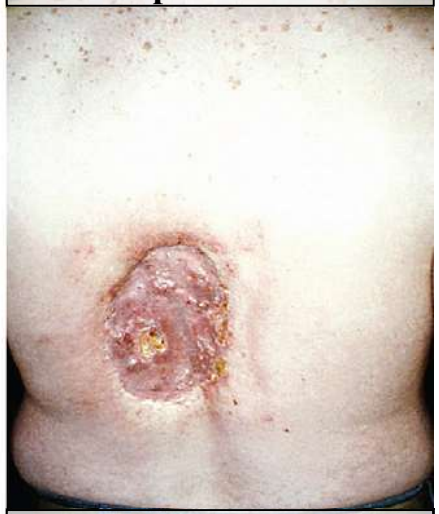


Erythema 6-8 weeks after last treatment



Loss of pigmentation at 16-21 weeks

Deep necrosis with atrophic borders



at 18-21 months

Balter S, Hopewell JW, Miller DL, Wagner LK, Zelefsky MJ. Fluoroscopically guided interventional procedures: a review of radiation effects on patients' skin and hair. Radiology. 2010 Feb;254(2):326-41.

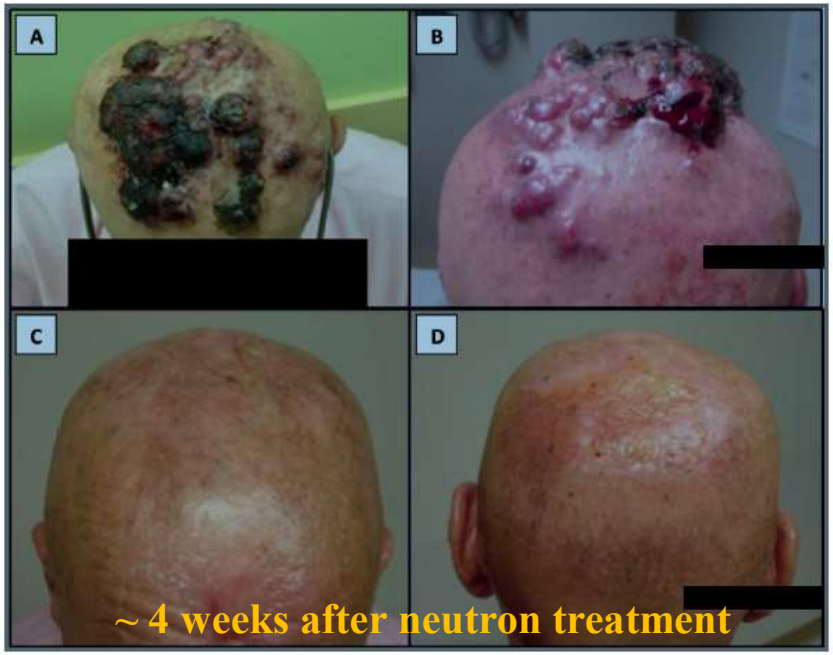
EQD2 for multiple FGI Procedures

- **Multiple procedures on same day separated by a few hours**
  - Repair of DNA damage over the course of even 2-6 hours is significant ($\tau \sim$ 1-2 h). In EBRT, tissue recovery can sometimes be significantly improved treating in at 9 am with a second treatment in the afternoon at 3 pm ("B.I.D. treatments")
- **Multiple procedures on different days spread over 2-8 weeks**
  - Repair of DNA damage on one day complete before damage caused by procedure on next day
  - Substantial, possibly full issue recovery and self-renewal post treatment, if total EQD2 < 50 Gy (i.e., keep accumulated EQD2 small enough to avoid late skin reactions)
- **Multiple procedures with at least > 8 weeks between procedures**
  - Maximizes recovery from early skin reactions
  - Minimizes potential for severe late skin reactions (necrosis and scarring)
  - **EBRT analogy – multiple courses of fractionated radiation therapy separated by weeks or months**

Recovery of the scalp after MV x-rays and Fast Neutrons

- **First diagnosed in February 2013. Multiple treatments through June 2015**
  - MV x-rays and electrons (EQD2 of 73.6 Gy to entire scalp, 91.2 Gy frontal scalp, 52 Gy left neck and parotid region)
  - Pembrolizumab, interferon to multiple scalp lesions, imiquimod to scalp, surgery
- **Treated with ~ 18 Gy fast neutrons in July 2015**
  - 18 Gy in 12 fractions (scalp), 18 Gy in 10 fractions (parotids/cervical lymph nodes), 16 Gy in 8 fractions (smaller isolated scalp lesions). **RBE ~ 5!**
- **Complete clinical and radiologic response without serious complications**
  - Mild telangiectasia, moderate xerostomia, decreased hearing on one side

Total EQD2 approaching 200 Gy!



Disease is still controlled 4 years later - Some small out of field recurrences responded to immunotherapy

Macomber M W, Tarabadkar E S, Mayr N A, Laramore G E, Bhatia S, Tseng Y D, Liao J, Arbuckle T, Nghiem P, Parvathaneni U 2017 Neutron Radiation Therapy for Treatment of Refractory Merkel Cell Carcinoma. Int. J. Part. Ther. 3(4) 485-491.

EQD2 for daily FGI procedures over few weeks?

Compute dose protraction factor and EQD2 for each procedure

$$G_{FBI} = \frac{2}{x^2}\left(e^{-x} + x - 1\right)$$

$$x \equiv \Delta T_{FGI} \cdot \ln 2 / \tau$$

τ ~ 1-2 h (half-time for DSB repair)

$$EQD2 = RWD \cdot \left(1 + \frac{RWD \cdot G_{FGI}}{\alpha / \beta}\right) / \left(1 + \frac{2\ \text{Gy}}{\alpha / \beta}\right)$$

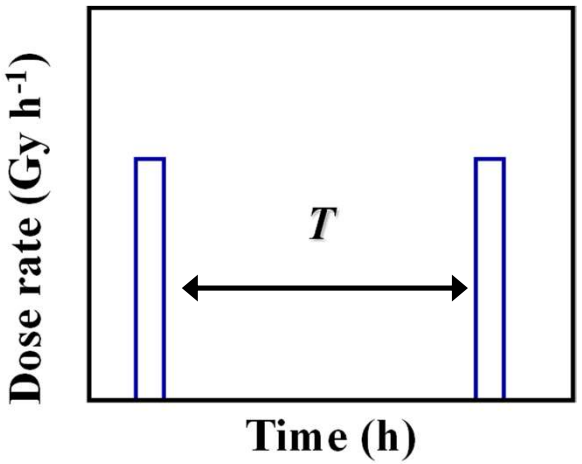
***RBE$_{DSB}$* ~ 1.2 to 1.3 (*soft kV x-rays*) to about 1.1 for heavily filtered (*hard*) kV x-rays (Stewart *et al.* 2015)**

Sum EQD2 for all *n* procedures (*effects of procedures are additive with little or no opportunity for tissue recovery and self-renewal over a few weeks*****)**

$$EQD2 = \sum_{i=1}^{n} EQD2_i$$

Analogous to EBRT of 25 × 2 Gy per day followed a few days later by a 5 × 2 Gy boost a few days later.

Split-Dose Experiments

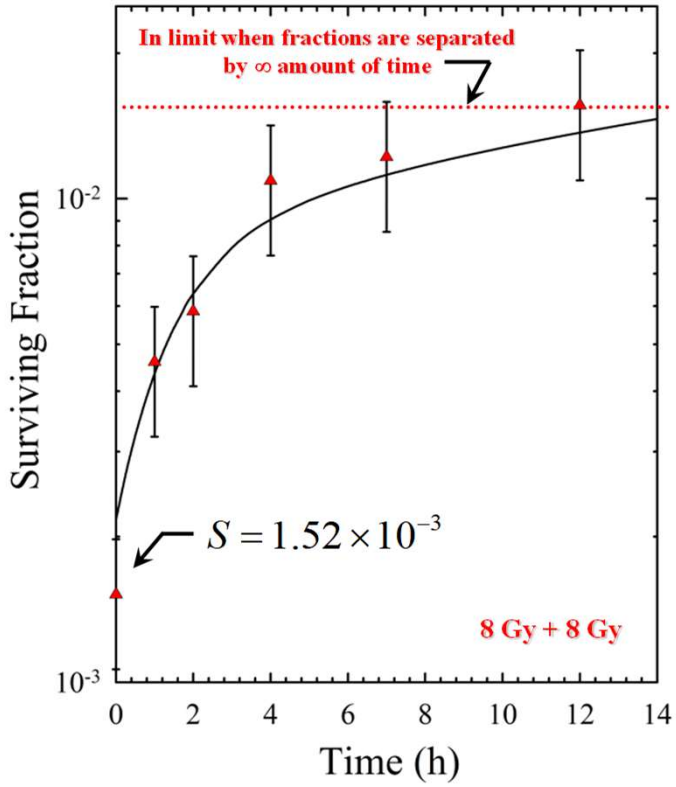


$$G = \frac{1}{2}(1 + e^{-x})$$

$$x = T \ln 2 / \tau$$

$$S(D) = \exp(-\alpha D - \beta G D^2)$$

Total dose *D*, fraction size *D*/2



EQD2 for 2 FGI procedures separated by few hours

Compute dose protraction factor and EQD2 for each procedure

$$G_{FGI} = \frac{2}{x^2}\left(e^{-x} + x - 1\right) \qquad EQD2 = RWD \cdot \left(1 + \frac{RWD \cdot G_{FGI}}{\alpha/\beta}\right) / \left(1 + \frac{2\ \text{Gy}}{\alpha/\beta}\right) \rightarrow d$$

$$x \equiv \Delta T_{FGI} \cdot \ln 2 / \tau$$

Compute EQD2 for combined morning + afternoon procedure and sum with correction for DSB repair between FGI procedures

$$EQD2 = D \cdot \left(1 + \frac{D \cdot G_{SD}}{\alpha/\beta}\right) / \left(1 + \frac{2\ \text{Gy}}{\alpha/\beta}\right) \qquad G_{SD} = \frac{d_1^2 + d_2^2 + 2d_1 d_2 e^{-x}}{\left(d_1 + d_2\right)^2}$$

$\mathbf{D = d_1 + d_2}$ $\qquad x = T \ln 2 / \tau$ $\qquad = \frac{1}{2}(1 - e^{-\lambda T})$ when $d_1 = d_2 = d$

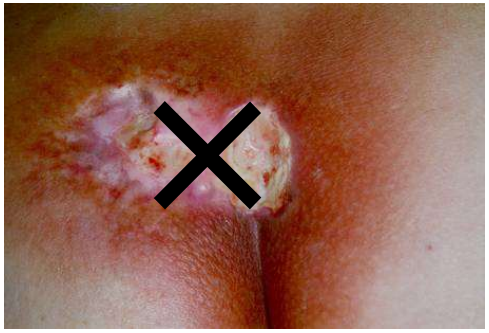
Summary and Conclusions

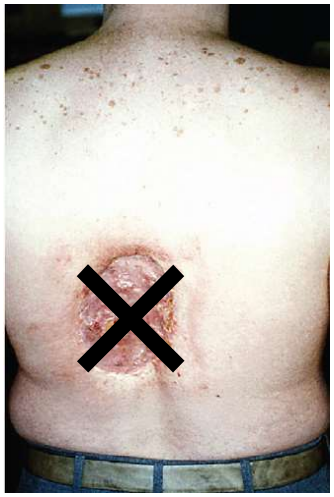
- **Considerable clinical experience and guidance available for conventional and hypofractionated external beam radiation therapy (EBRT)**
- **Biological metrics, such as EQD2, are a useful and convenient way to provide quantitative guidance for single- and multiple FGI procedures**
  - Corrections for intra- and inter-procedure dose rate (DNA repair) effects, RBE of kV x-rays relative to MV x-rays and fraction size (dose per procedure) are important and easily modeled
- **Addition work is needed to model and validate other tissue recovery mechanisms (**cell proliferation, migration, differentiation, effects of vascular injury, …**) that operate over time scales of days to weeks**
- **Need to move towards improved accuracy of dose to tissue at relevant depths (**e.g., 70 μm and 1 mm**) with corrections for off-axis (**heel**) effects**

Thank you

- For a copy of the handouts or presentation slides, contact me at **trawets@uw.edu**

$$EQD2 = RWD \cdot \frac{\left(1 + \frac{RWD \cdot G_{FGI}}{\alpha / \beta}\right)}{\left(1 + \frac{2\ \text{Gy}}{\alpha / \beta}\right)}$$





A little bit of math and the judicious application of a few R's of radiation biology has the potential to impact patient care (*help avoid serious toxicity*).