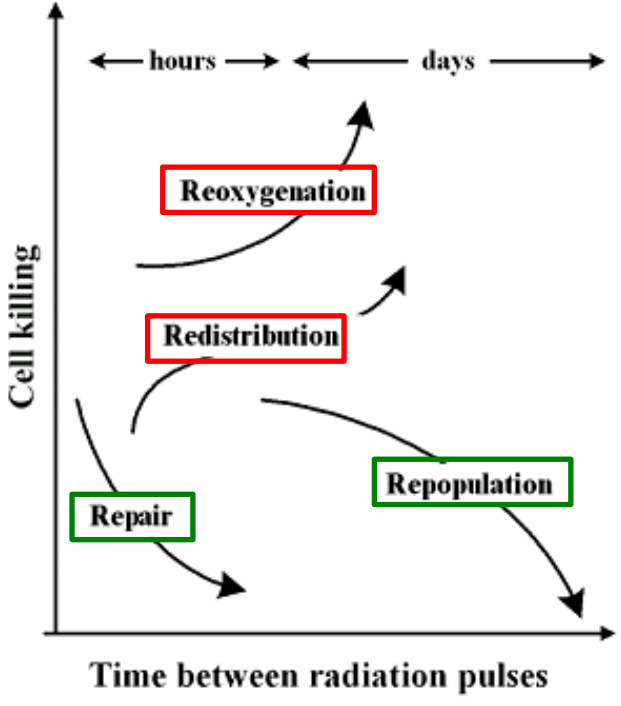
Chapter 23 – Time, Dose & Fractionation Lecture 2

12/5/2024

Basis of Fractionation



Fractionation spares normal tissue

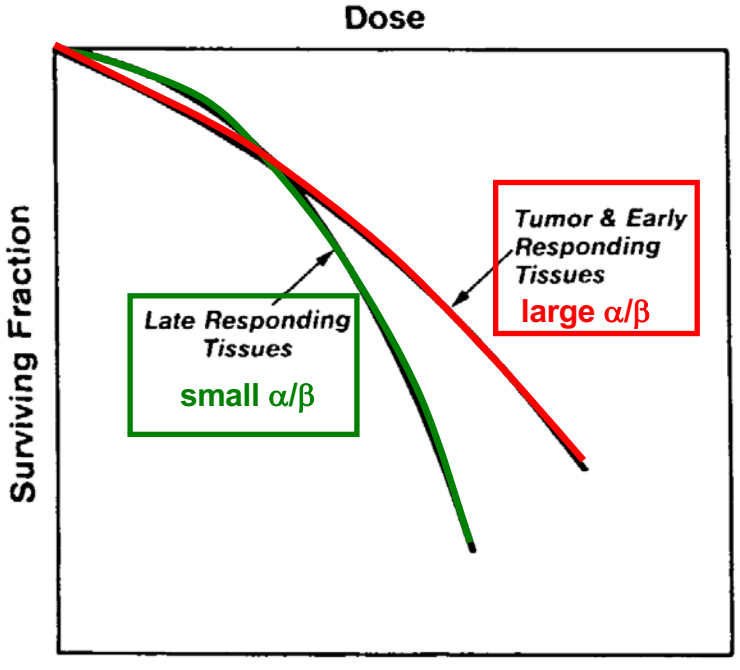
Repair of sublethal damage
Repopulation of normal cells (early-responding tissue)

Fractionation increases tumor kill

Reoxygenation
Reassortment of cells into more radiosensitive phase

There is a **fine balance** – excessive fractionation/prolongation of treatment allows surviving tumor cells to proliferate during the treatment!

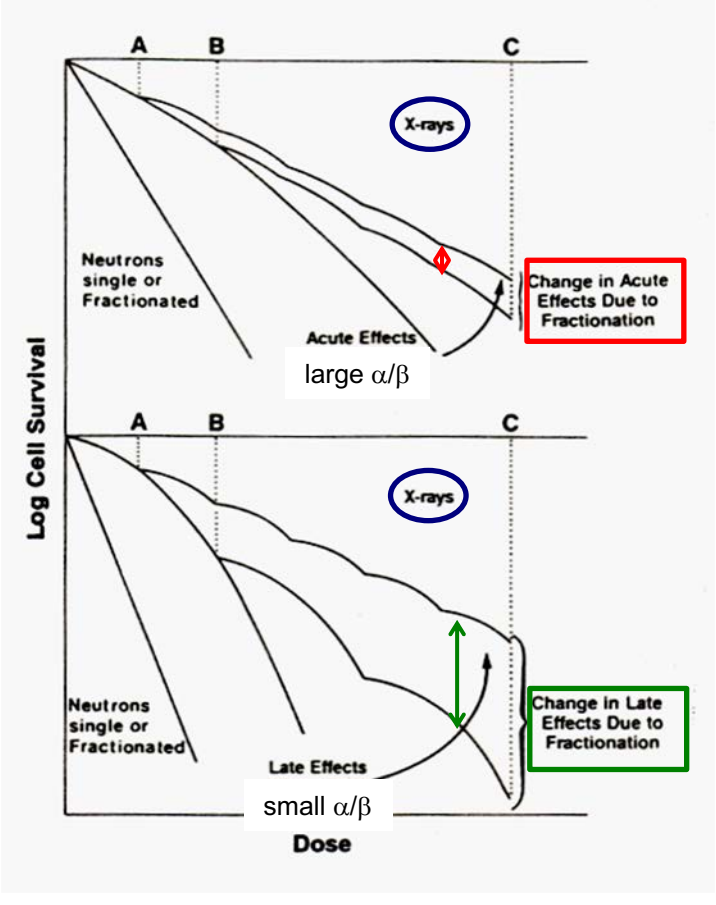
Dose-Response Curve – Early vs. Late-Responding Tissue



The dose-response relationship for late-responding tissue is **curvier** than for early-responding tissues

In the linear-quadratic formulation, this translates into a larger α/β ratio for early effects than for late effects

Effect of Fractionation



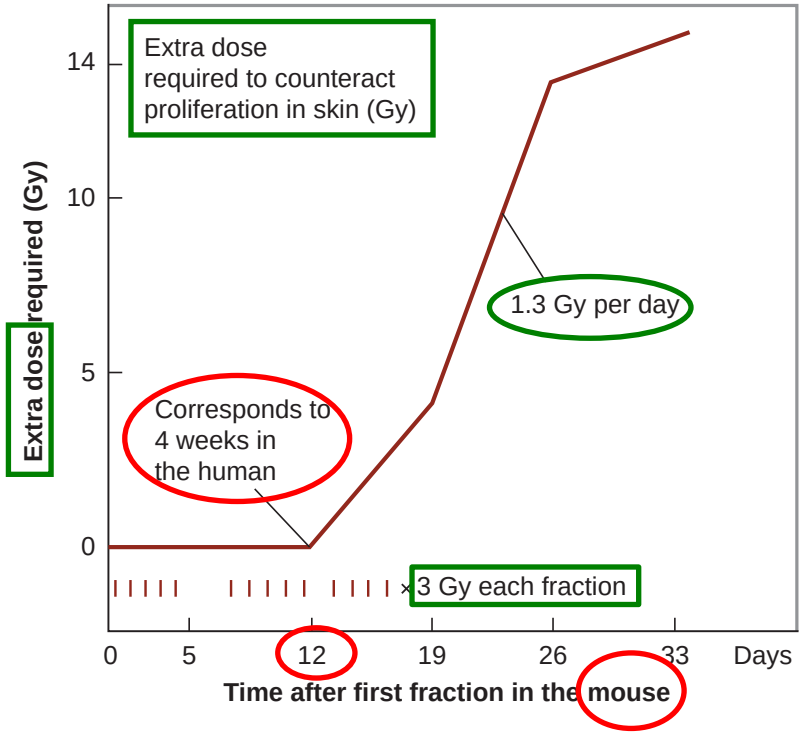
Fraction size is a dominant factor in determining **late effects**, more so than for early effects

Shoulder has to be repeated with each fraction

Multifractionation leads to more sparing of the late effects than early effects

Related to lengthening of treatment time

Proliferation Factor

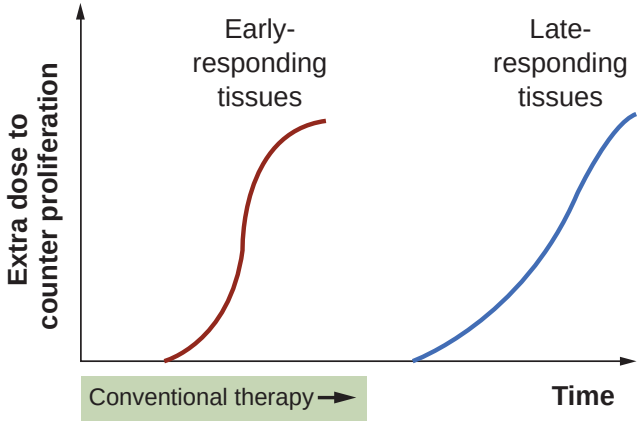


The shape of the curve is roughly **sigmoidal** – a delay followed by rapid increase (<u>at which point, skin is triggered to proliferate</u>)

In mouse, the delay is about 2 weeks

In **humans**, it is about **4 weeks** because of the slower response of the human skin and the longer cell cycle of the individual cells

Effect of Treatment Time



"Prolonging overall treatment time spares **Early**- but not **Late**-responding tissues"

Early Effects

Protracting overall treatment time beyond the conventional 6-8 weeks may result in sparing of normal tissue (e.g., skin reaction, mucositis)

[But tumors may also be spared]

Decreasing overall treatment time to less than the conventional 6-8 weeks may result in more acute normal tissue reactions

Late Effects

Treatment time has relatively little effect on responses in late effects tissues

Outline

- Historical Perspective of Fractionation
- The Strandquist Plot and the Ellis NSD System
- Fraction Size – Early vs. Late-Responding Tissues
- Overall Treatment Time
  - Proliferation as a Factor in Normal Tissues
  - Accelerated Repopulation in Tumor
- **Clinical Exploitation**
  - Hyperfractionation
  - Accelerated Treatment
  - CHART
  - ARCON
  - Hypofractionation
- BED Calculation Based on Linear-Quadratic Model

Strategies to Improve Therapeutic Ratio

Conventional Fractionation – 1.8 - 2.2 Gy /fraction; 5 fractions per week; total dose of 50-65 Gy

Hyperfractionation – by delivering a smaller dose per fraction, the intent is to further reduce the late effects

Accelerated Fractionation – by delivering two doses of radiation daily, the intent is to reduce repopulation in rapidly proliferating tumors

Hyperfractionation

Basic Design

Deliver smaller dose per fraction twice (or more) per day
The total dose will have to be increased because the dose per fraction is decreased

Intent

To further separate early and late effects, i.e., reduce late effects and achieve the same or better tumor control and the same or slightly increased early effects
Used when late normal tissue tolerance is a concern

Example

Conventional – 70 Gy in 35 fractions, 2 Gy per fraction per day (QD), 7 wks
Hyperfractionation – 80.5 Gy in 70 fx, 1.15 Gy per fraction twice per day (BID), 7 wks

Hyperfractionation – EORTC 22791

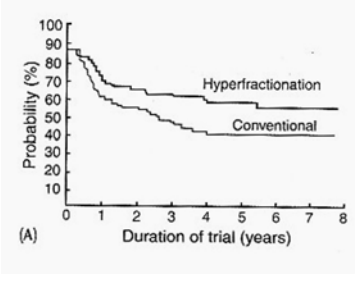
Intermediate stage oropharyngeal ca

®

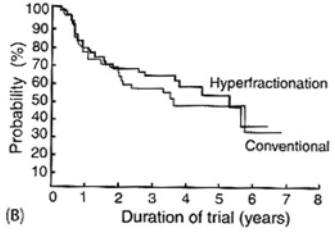
- 70 Gy/35 fx/7 wks (2 Gy QD)
- Prospective randomized trial
- 80.5 Gy/70 fx/7 wks (1.15 Gy BID)

Outcome

- 5-year local control rate significantly better – 59% vs. 40%
- A trend toward improved survival
- More acute mucositis
- No difference in late complication rate



Local control



Late effects

Horiot 1992

Accelerated Fractionation

Basic Design

"Pure" – same dose per fraction delivered twice (or more) per day, so the overall time is reduced
Because the acute side effects becomes limiting, it is necessary to either interpose a rest period in the middle of the course (split-course) or to reduce the dose slightly

Intent

To reduce repopulation in rapidly proliferation tumor
Theoretically, there should be little or no change in the late effects, because the # of fractions and the dose per fractions are unaltered (if SLD repair is complete between fractions)

Example

Accelerated Treatment – 72 Gy in 45 fx, 1.6 Gy per fraction 3x per day, 5 wks

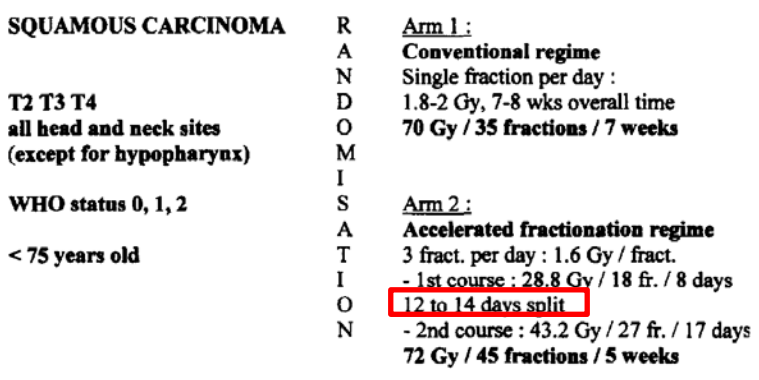
Accelerated Fractionation – EORTC 22851

512 patients with T2-T4 H&N cancer

®

70 Gy/35 fx/7 wks (2 Gy QD)

72 Gy/45 fx/5 wks (1.6 Gy TID) split course



SQUAMOUS CARCINOMA

T2 T3 T4
all head and neck sites
(except for hypopharynx)

WHO status 0, 1, 2

< 75 years old

RANDOMISATION

Arm 1 :
Conventional regime
Single fraction per day :
1.8-2 Gy, 7-8 wks overall time
70 Gy / 35 fractions / 7 weeks

Arm 2 :
Accelerated fractionation regime
3 fract. per day : 1.6 Gy / fract.
- 1st course : 28.8 Gy / 18 fr. / 8 days
12 to 14 days split
- 2nd course : 43.2 Gy / 27 fr. / 17 days
72 Gy / 45 fractions / 5 weeks

Fig. 1. Trial design.

Horiot 1997

Accelerated Fractionation – EORTC 22851

Outcome

- 5-year local control rate significantly better – 15% improvement
- A trend toward improved survival
- Acute side effects significantly increased (expected)
- Late severe functional damage – 14% vs. 4% (including fatal complication)

Acute Toxicity

Table 4
Acute toxicity

Grades 3–4	No. of patients (%)	
	CF arm (n = 245)	AF arm (n = 240)
FMR during treatment	111 (45)	162 (68)
OMR during treatment	123 (50)	160 (67)
FMR 6 weeks after treatment	72 (29)	154 (64)
OMR 6 weeks after treatment	84 (34)	168 (70)
Life threatening (14 weeks after treatment)	5 (2)	13 (5)

FMR, functional mucosal reactions reported by the patients.
OMR, objective mucosal reactions scored by the physician.
Analysis November 1995.

Late Toxicity

- Severe neurological complications were observed only in the AF arm, consisting of seven cases of permanent peripheral neuropathy and two cases of radiation-induced myelitis
- Severe fibrosis occurred in 29 cases in the AF arm and in 4 cases in the CF arm

Accelerated Fractionation

Several other trials also compared accelerated fractionation with conventional regimen

These trials kept the total dose as high as 66-72 Gy, but shorten the overall time by as much as 2-3 wks

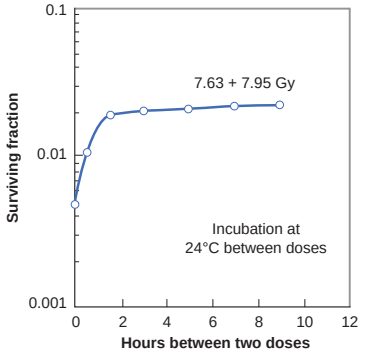
All of these trials showed serious late complications with accelerated treatment, likely due to

1. **"consequential late damage"**
2. **Incomplete SLD repair** b/w fractions – only 4-hour interval in EORTC trial

Pure accelerated treatment must be used with extreme caution!!!

Time Interval Between Multiple Daily Fractions

With cells cultured ***in vitro***, the half-time of repair of SLD is estimated to be **1 hr** from split dose experiment



For normal tissues ***in vivo***, it has been inferred from fractionation experiments that the repair of SLD may be very **much slower** in late-responding tissues

Results from **clinical trials** clearly indicated that 4 hours is insufficient, and even **6 hours may not be adequate** for spinal cord → SLD repair is very slow in late-responding tissues; this is radiobiology learned from the clinic!

CHART

CHART – **C**ontinuous **H**yperfractionated **A**ccelerated **R**adiation **T**herapy

Rationale

Hyperfractionation – to minimize late effects
Accelerated treatment – to minimize tumor proliferation

Example

54 Gy/36 fractions, 1.5 Gy 3 x per day (6 hours apart), 12 consecutive days

CHART – UK Trial

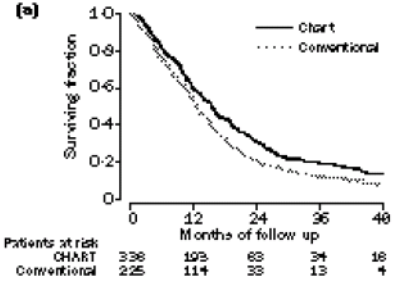
563 patients with non-small cell lung cancer

®

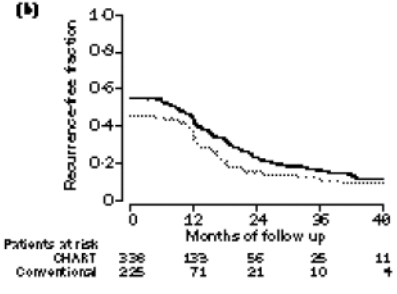
60 Gy/30 fx/6 wks (2 Gy QD)

54 Gy/36 fx/12 days (1.5 Gy TID)

Significant improvement in outcome



Survival



Local control

CHART – UK Trial

Acute Toxicity (initial 3 months)

Esophagitis – occurred sooner and was more severe in the CHART patients
Pneumonitis – marginally greater in the conventionally treated cases

Intermediate Toxicity

Lhermittes sign – recorded in 8 patients, all treated with CHART; all resolved [perhaps due to inadequate SLD repair between fractions]

Late Toxicity

No significant difference in pulmonary fibrosis or esophageal stricture

ARCON

ARCON – Accelerated Hyperfractionated Radiation Therapy while Breathing Carbogen and with the Addition of Nicotinamide

Rationale

Accelerated treatment – to minimize tumor proliferation
Hyperfractionation – to minimize late effects
Carbogen breathing – to overcome chronic hypoxia
Nicotinamide – overcome acute hypoxia

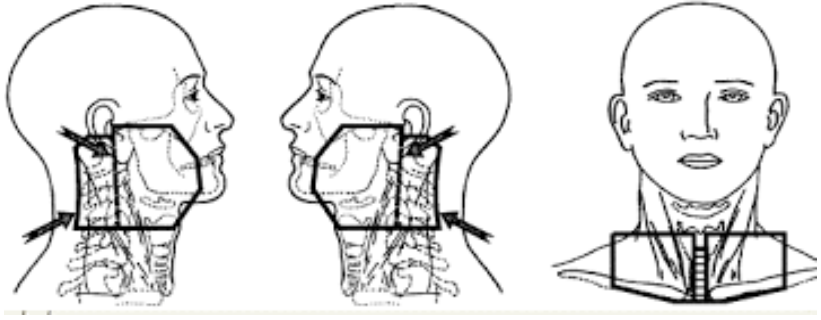
ARCON: accelerated radiotherapy with carbogen and nicotinamide in head and neck squamous cell carcinomas. The experience of the Co-operative Group of Radiotherapy of the European Organization for Research and Treatment of Cancer (EORTC)☆

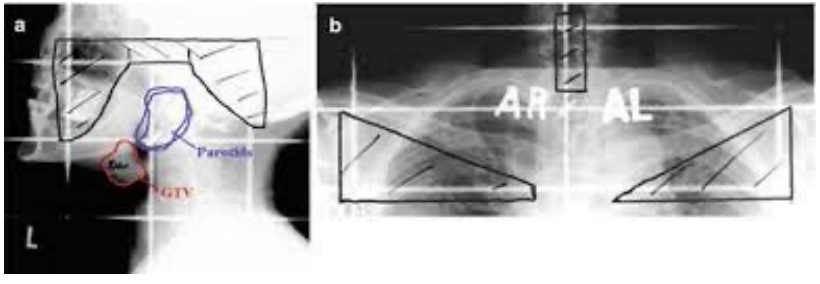
Jacques Bernier[a,*], Juliana Denekamp[b], Anamaria Rojas[c], Emilio Minatel[d], Jean-Claude Horiot[e], Han Hamers[f], Paolo Antognoni[g], Olav Dahl[h], Pierre Richaud[i], Martine van Glabbeke[j], Marianne Piérart[j]

RADIOTHERAPY & ONCOLOGY

Conclusion: Future ARCON trials should target selected head and neck tumor localizations and stages, and a lower nicotinamide dose is needed to reduce severe upper gastro-intestinal toxicity.

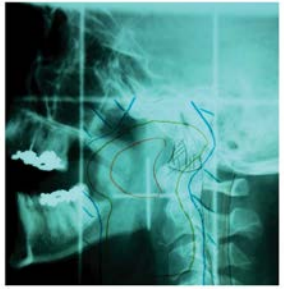
Evolution of H&N Radiation Therapy



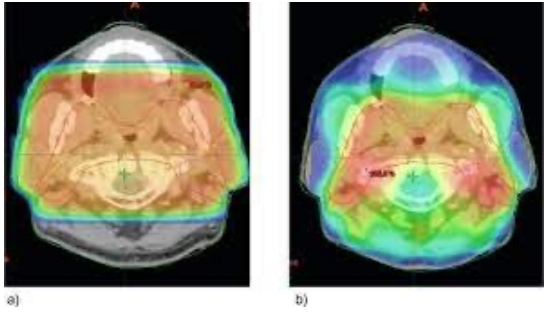


Spinal cord receives full dose from R and L lateral beams

Off cord boost

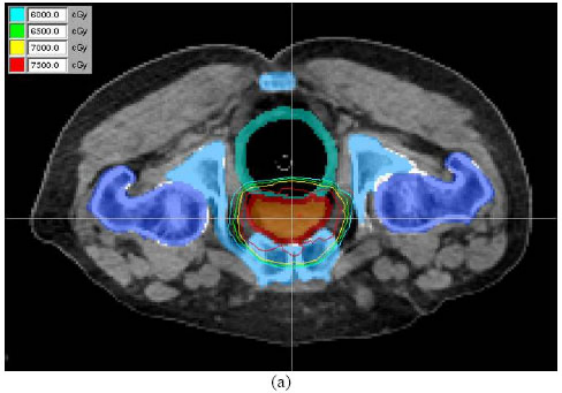


IMRT spares cord



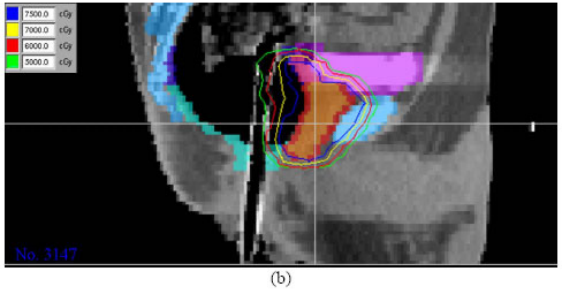
Hypofractionation

Recently, there is a renewed interest in dose fraction larger than 2 Gy for curative radiotherapy; this is known as **hypofractionation**



(a)

Hypofractionation is now increasingly being used for both curative and salvage radiotherapy



(b)

Let's study the special case of prostate cancer

Hypofractionation

Unlike rapidly proliferating tumors such as H&N cancer, prostate does not behave like a typical acute-responding tissue

Regression of prostate cancer following radiotherapy is **slow** (evidenced both by biopsy and PSA decline)

Cell proliferation kinetics reflect **slow cell replication rate**

a. Labeling index $\leq$ 2%
b. T_{pot} about 40 days
c. Tumor growth rate is sufficiently slow in many men that watchful waiting is an acceptable option

The α/β for prostate cancer is in the region of **2-3 Gy** (some studies report value as low as **1.2 Gy**)

Implications of Low α/β Ratio

Both tumor and late-responding tissues have similar α/β ratio

⇩

Both tumor and late-responding tissues have similar sensitivity to changes in fractionation

⇩

There is no advantage to therapeutic ratio for late reactions for multiple small fractions

To Stir the Pot!

Current data suggest that the α/β of rectum is between 4-5 Gy and that the value for prostate cancer may be closer to 1.5-2 Gy

If this is true, hypofractionation offers the potential to markedly increase the total delivered dose without compromising the late rectal toxicity AND still deliver a non-toxic dose to the acute response normal tissues

Defining the Terms

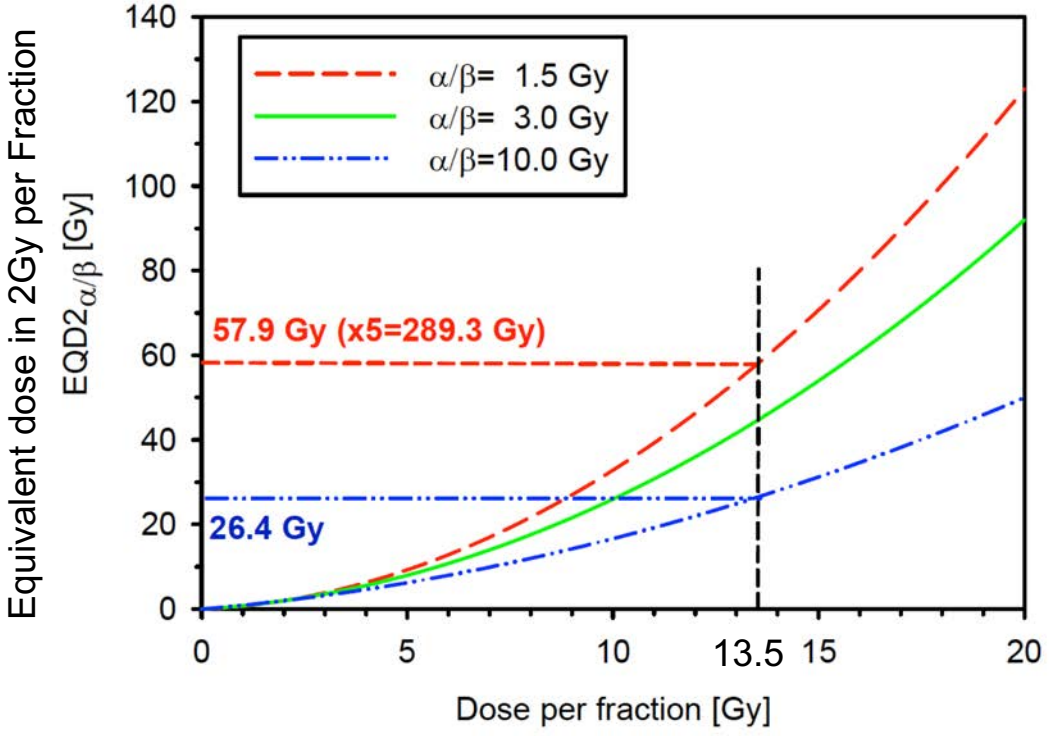
Term	Definition
SRS	Stereotactic radiosurgery; a single fraction to the brain
SBRT	Stereotactic body radiotherapy
SABR	Stereotactic ablative radiotherapy

Essentially the same and refer to tumors outside the brain treated 1-5 fractions

Examples:
- 75 Gy in 2.5 Gy/fx over **5 weeks**
- 67.5 Gy in 13.5 Gy/fx over **2 weeks**

Both imply not just a biological change in terms of **fraction size effect**, but inherently often build in **accelerated radiotherapy** delivery

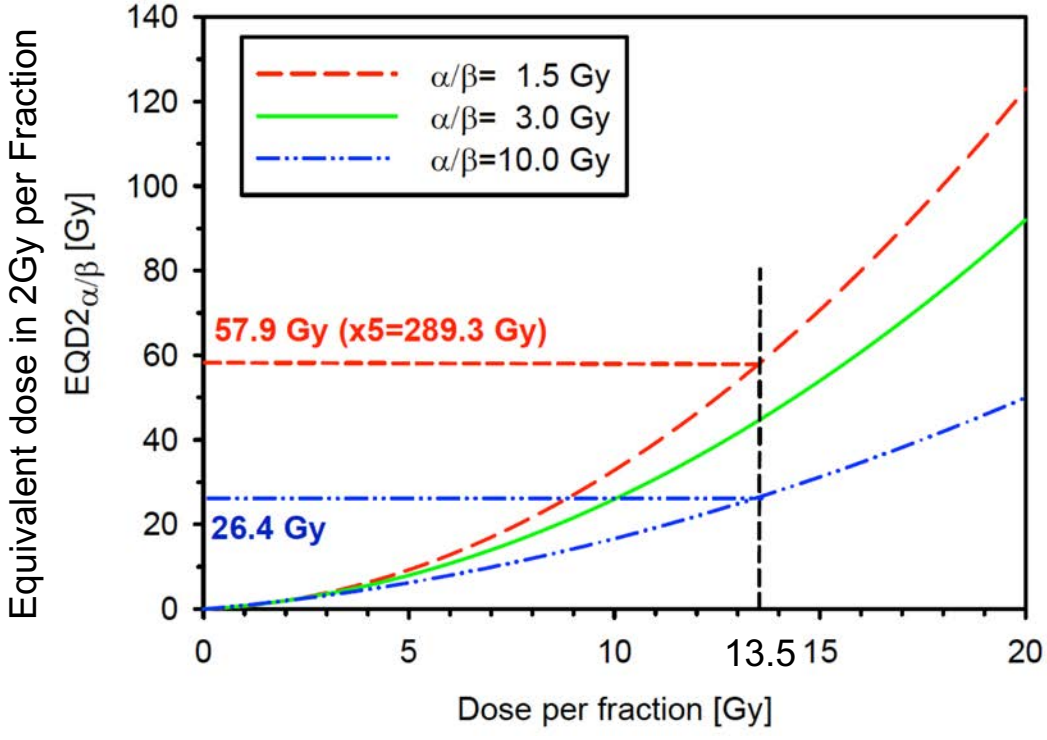
Dose per Fraction and α/β Ratio



Tissues are less capable of performing repair if the fractional dose is higher

With fewer fractions, less total dose is necessary for the same effect

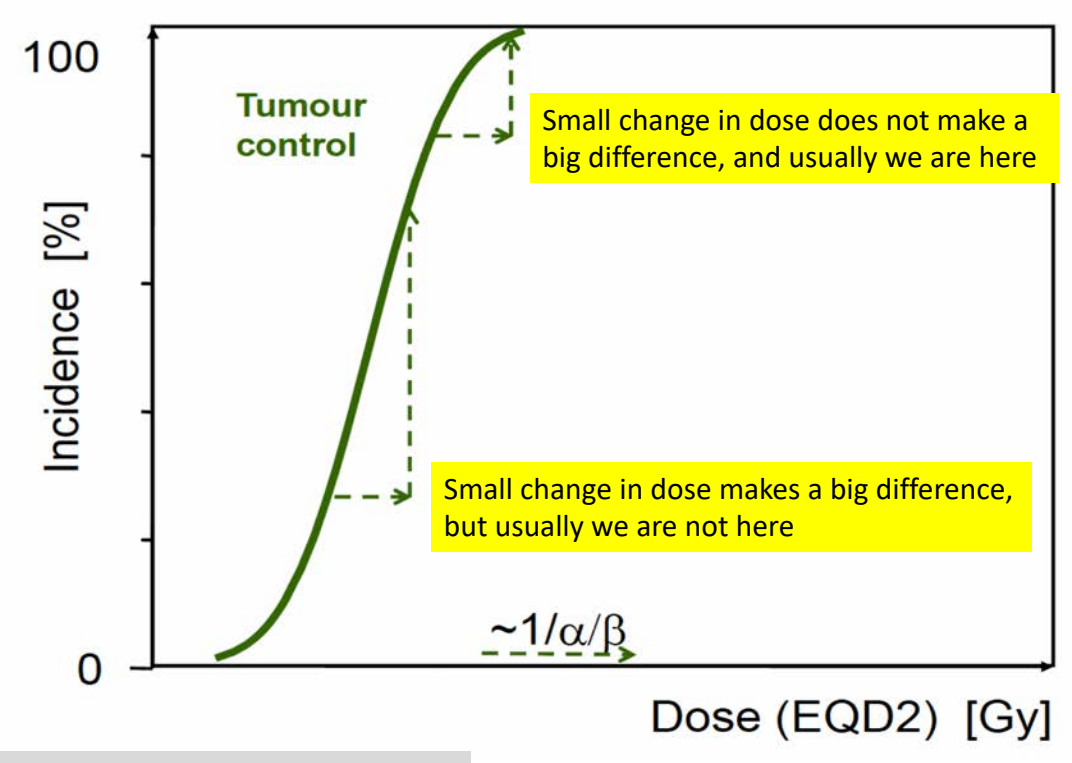
Dose per Fraction and α/β Ratio



However, this effect is different for different tissues, a function of the "repair-capacity", reflected in the linear quadratic model

Tissue with lower α/β values are substantially more susceptible to large fractions!

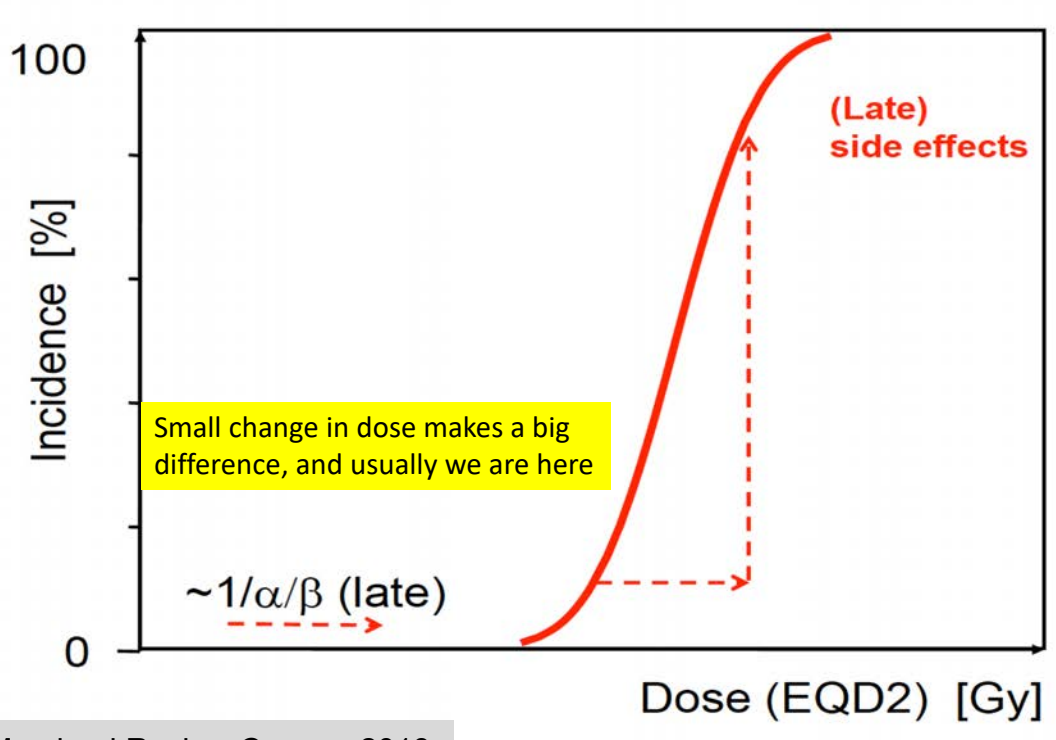
Dose Response Relationship – Tumor



Beyond α/β, where you are on the slope makes a huge difference

When the total dose is high enough, you don't gain much by escalating the dose further

Dose Response Relationship – Late Responding Normal Tissue



Small change in dose could substantially increase toxicity

Maryland Review Course, 2018

Technologic Advance

Besides radiobiological factors, technologic advance in radiation delivery also made hypofractionation an attractive possibility

The development of IMRT, tomotherapy and proton beam results in greatly improved dose distributions, with more limited doses to normal tissues for comparable tumor doses → the need to spare late responding normal tissues by fractionation is reduced

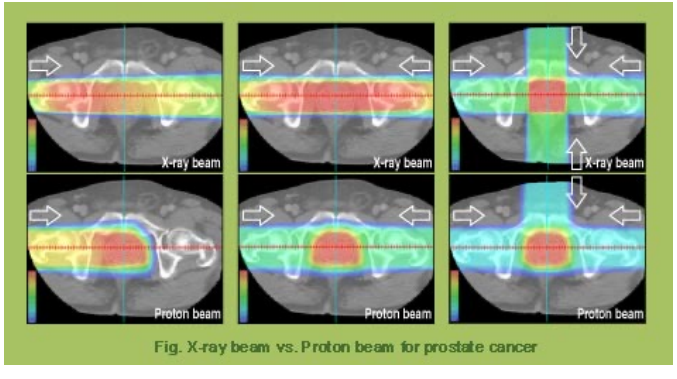
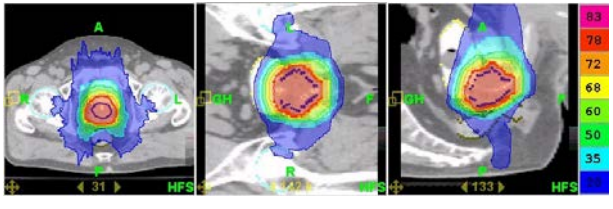


Fig. X-ray beam vs. Proton beam for prostate cancer



What Else is Going with Hypofx?

- Vascular collapse?
- Immune stimulation?

Stay Tuned!

		The Possibilities of the Perils	
12/9	M	Guest Lecture: Hyperthermia; Radiobiology of SBRT, SFRT and FLASH	Song
12/12	Th	Chapter 26: The Biology and Exploitation of Tumor Hypoxia	Yuan
12/16	**Th**	**Exam 3 (Cumulative; 40%)**	**Yuan/Sloan**

Hypofractionation in the Clinic

- **Inherently dangerous because of greater impact on late reacting normal tissues**
  - Requires very precise dose delivery
  - More precise dose delivery leads to dose compression and higher partial volume OAR doses/fx, resulting in novel side effects
- **Advantages for tumor control**
  - From the perspective of acceleration
  - Possibly immune enhancement & vasculcar damage (Dr. Song' lecture)
- **Vascular effects could be a double-edged sword**
  - Higher tumor control
  - Possibly also higher complications

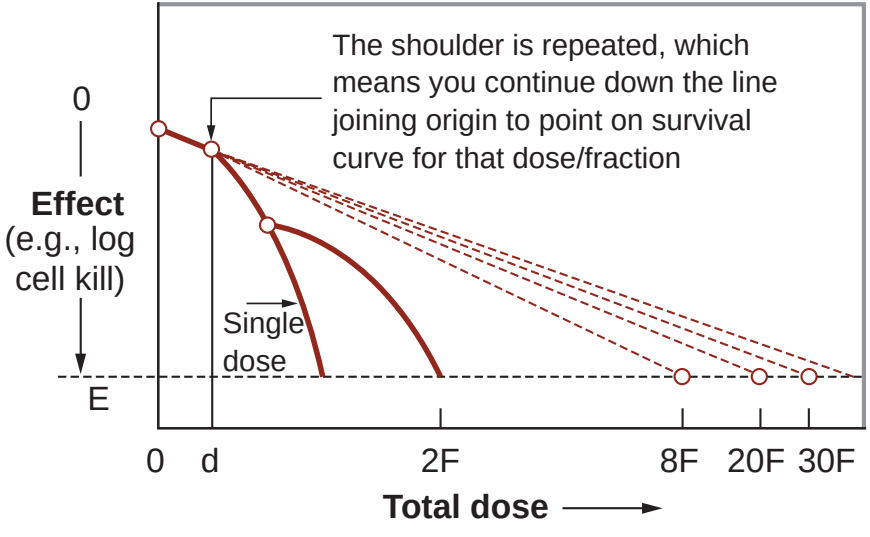
Outline

- Historical Perspective of Fractionation
- The Strandquist Plot and the Ellis NSD System
- Fraction Size – Early vs. Late-Responding Tissues
- Overall Treatment Time
  - Proliferation as a Factor in Normal Tissues
  - Accelerated Repopulation in Tumor
- Clinical Exploitation
  - Hyperfractionation
  - Accelerated Treatment
  - CHART
  - ARCON
  - Hypofractionation
- **BED Calculation Based on Linear-Quadratic Model**

The Linear-Quadratic Model

Clinically, it is often useful to **compare different fractionation regimens**
The **Ellis NSD system** was created for such purpose, and was in use for many years

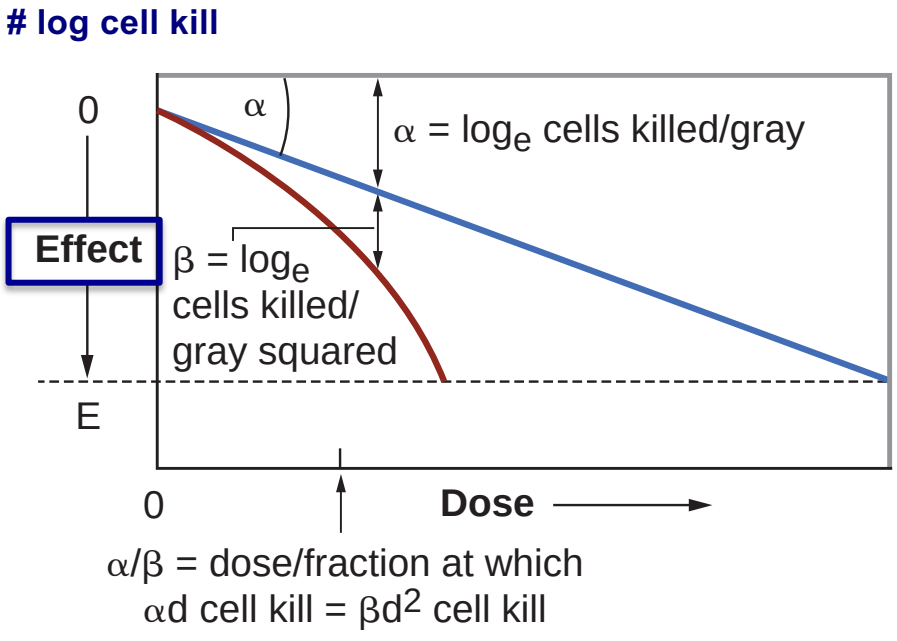
The **linear-quadratic model** has now received greater acceptance



Single dose is linear-quadratic

Effective dose-response curve for multifraction regimens approaches an exponential function of dose

The L-Q Equation



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

$$\ln S = -\alpha D - \beta D^2$$

 # log cell kill

α is the # of logs of cell kill **per Gy** from the linear portion of the curve

β is # of logs of cells kill **per Gy^2** from the quadratic component

The L-Q Equation

For a single acute dose D, the biologic effect (**logs of cell kill**) is given by

$$E = \alpha D + \beta D^2$$

If dose **D** is separated into **n** fractions of dose **d**, the biologic effect of d is given by

$$e = \alpha d + \beta d^2$$

n fractions of dose **d**,

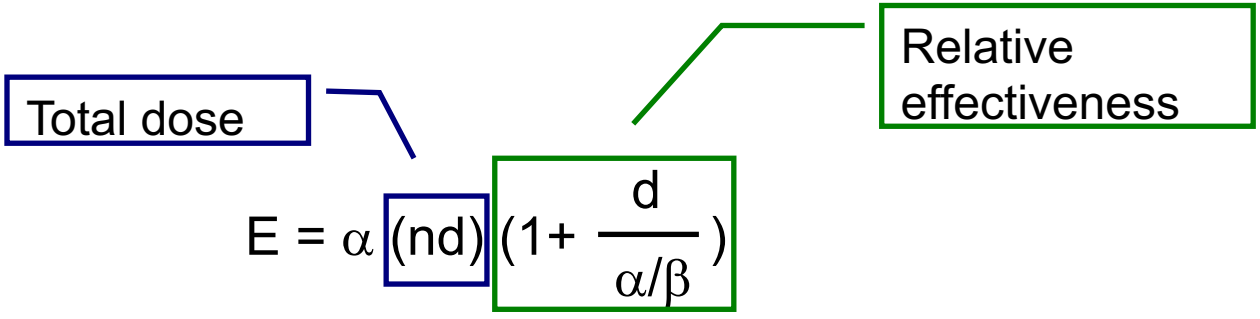
$$E = n(\alpha d + \beta d^2)$$

(Multifraction regimen)
Contribution of each fraction d is the same

Rewrite the equation

$$E = (nd)(\alpha + \beta d) = \alpha\,(nd)\,(1+ \frac{d}{\alpha/\beta})$$

The L-Q Equation



Divide by α, we have

Biologically effective dose (BED)

$$\frac{E}{\alpha} = (nd)\,(1+ \frac{d}{\alpha/\beta})$$

BED equation

or

α/β equation

Note that BED has the unit of Gy, because E is logs of cell kill, and α is the log cell kill per Gy

Choice of α/β

Assumption

α/β **= 10 Gy** for early-responding tissues (including tumor)
α/β **= 3 Gy** for late-responding tissues

Other values could be used if more appropriate

Utility of LQ Equation

By using different values of α/β, the LQ model emphasizes the difference between early- and late-responding tissues

It should be noted that while we can use the equation to compare early effects or late effects between two regimens, **it is not possible or meaningful to compare early with late effects**

It is also not possible to match two different fractionation regimens to be equivalent for both early and late effects

Example 1 – Conventional Fractionation

Question

What is the BED for conventional treatment that consists of 35 fractions of 2 Gy given once daily, 5 days per week, for an overall treatment time of 7 weeks? (i.e, 35F x 2 Gy/7 wks) [note that textbook used 30F x 2 Gy/6 wks, which falls short of what we typically use for H&N cancer]

Solution

First, it is important to recognize that the BED for early effects and late effects have to be calculated separately!!!

Early effects: $\frac{E}{\alpha} = (nd)\left(1+\frac{d}{\alpha/\beta}\right) = 70\left(1+\frac{2}{10}\right) = \mathbf{84}\ Gy_{10}$

Late effects: $\frac{E}{\alpha} = (nd)\left(1+\frac{d}{\alpha/\beta}\right) = 70\left(1+\frac{2}{3}\right) = \mathbf{116.9}\ Gy_{3}$

Example 2 – Hyperfractionation

Question

What is the BED for a hyperfractionated regimen 70F x 1.15 Gy twice daily/7 wks?

Solution

Early effects: $\frac{E}{\alpha} = (nd)\left(1+\frac{d}{\alpha/\beta}\right) = 80.5\left(1+\frac{1.15}{10}\right) = \mathbf{89.8}\ Gy_{10}$

Late effects: $\frac{E}{\alpha} = (nd)\left(1+\frac{d}{\alpha/\beta}\right) = 80.5\left(1+\frac{1.15}{3}\right) = \mathbf{111.4}\ Gy_{3}$

Note that this is a “hotter” regimen than the conventional 70 Gy for early effects, but “cooler” for late effects

$= \mathbf{84}\ Gy_{10}$

$= \mathbf{116.9}\ Gy_{3}$

Example 3 – Concomitant Boost

Question

What is the BED for an accelerated regimen with concomitant boost: 30 fractions of 1.8 Gy once every morning, 5 days a week, and on the last 12 days, a boost to smaller field in the afternoon (6 hours from the am dose), 1.5 Gy per fraction; i.e., [30F x 1.8 Gy] + [12F x 1.5 Gy]/6 wks?

By giving the boost concomitantly, a prolongation of overall time is avoided

Note that parts of schedules can be added, i.e, BED = $(\text{partial effect})_1$ + $(\text{partial effect})_2$

Example 3 – Concomitant Boost

Solution

Early effects: $1.8 \times 30 \left(1 + \frac{1.8}{10}\right) + 1.5 \times 12 \left(1 + \frac{1.5}{10}\right) = \mathbf{84.4}\ Gy_{10}$

Late effects: $1.8 \times 30 \left(1 + \frac{1.8}{3}\right) + 1.5 \times 12 \left(1 + \frac{1.5}{3}\right) = \mathbf{113.4}\ Gy_{3}$

You should work out the other two examples given in the Hall book, i.e., accelerated fractionation and CHART

Example 4 – Hypofractionation

Question

What is the total dose required to produce equivalent **tumor effect** and **late effect** as 36F x 2 Gy if dose is delivered in 4 Gy per fractions for prostate cancer?

Solution

Assume α/β = 3.0 Gy for prostate cancer and late effect

BED (conventional) = $36 \times 2 \times \left(1 + \frac{2}{3}\right) = 120\ Gy_3$

BED (hypofractionation) = $120\ Gy_3 = \mathbf{n} \times 4 \times \left(1 + \frac{4}{3}\right) \rightarrow \mathbf{n} = 13 \rightarrow$ Total dose = $13 \times 4 = 52\ Gy_3$

Therefore, 4Gy/fx to 52Gy is predicted to result in equivalent prostate tumor control AND late normal tissue reactions as the conventional schedule

Example 4 – Hypofractionation

Question

What is the effect of the hypofractionated schedule on **acute normal tissue reactions**?

Solution

Assume α/β = 10 Gy for acute effects

$$\text{BED (conventional)} = 36 \times 2 \times \left(1 + \frac{2}{10} \right) = 86\ \text{Gy}_{10}$$

$$\text{BED (hypofractionation)} = 13 \times 4 \times \left(1 + \frac{4}{10} \right) = 73\ \text{Gy}_{10}$$

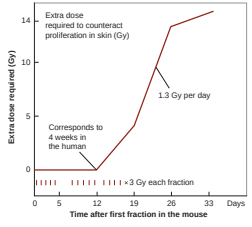
Therefore, with hypofractionation, the acute normal tissue damage is predicted to be LESS than that with the conventional schedule!

Allowance for Tumor Proliferation

The BED equation $\frac{E}{\alpha} = (nd)\left(1+\frac{d}{\alpha/\beta}\right)$ does not account for tumor proliferation, therefore, to be more accurate, corrections need to be made

Calculation suggested by Fowler assumes that the rate of cellular proliferation remains constant throughout the overall treatment time

$$E = n(\alpha d + \beta d^2) - 0.693\,\frac{t}{T_{pot}}$$



$$BED = \frac{E}{\alpha} = (nd)\left(1+\frac{d}{\alpha/\beta}\right) - \frac{0.693}{\alpha}\,\frac{t}{T_{pot}}$$

t is the # of days available for proliferation

Example 5 – Correction for Tumor Proliferation

Question

How much would the BED be reduced due to tumor proliferation for a typical 6-wk (39 day) schedules?

Solution

Rapid proliferation does not start up until about **21-28 days** after treatment begins → t = 39 - 21 = 18 days

It is also necessary to assume a value for α, the initial slope of the cell survival curve, as well as for T_{pot} – a reasonable value for α is 0.3 ± 0.1/Gy; T_{pot} may have a value of 2-25 days with a median value of 5 days

$$\frac{E}{\alpha} = \frac{0.693}{0.3} \times \frac{(39-21)}{5} = 8.3\ Gy_{10}$$

Effect of Tumor Proliferation on Various Treatment Regimens

Protocol	E/α Early, i.e., Tumor, Gy_{10}	Proliferation Correction, Gy_{10}	Corrected for Time Gy_{10}
Conventional protocol: 30F x 2 Gy/6 wk (39 d)	72	-8.3	63.7
Conventional protocol: 35F x 2 Gy/6 wk (46 d)	84	-11.6	72.4
Hyperfractionation: 70F x 1.15 Gy/7 wk (46 d)	89.8	-11.6	78.2
Concomitant boost: (30F x 1.8 Gy) + (12F x 1.5 Gy)/6 wk (39 d)	84.4	-8.3	76.1
CHART: 36F x 1.5 Gy/12d	62.1	0	62.1

This correction for time assumes T_p = 5 days, T_K= 21 days, and α = 0.3 per Gy

Note that rapid proliferation has not started by the time the treatment is completed

Pragmatic Approach of Peters

The previous method of correction for treatment time makes several assumptions, and cumbersome to use

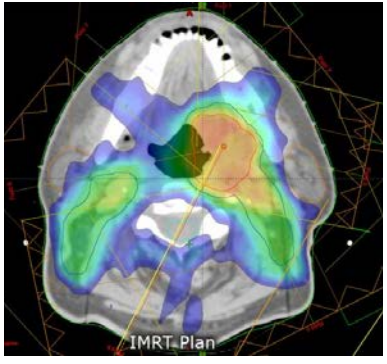
Pragmatic Approach

Peters *et al.* in Australia have taken the pragmatic approach that between **5 and 7 weeks** after the start of fractionated regimen, the dose equivalent of regeneration with protraction of treatment is about **0.5 Gy per day**, rounded down to **3 Gy per week**

Implications in H&N IMRT Regimen

For H&N cancer, different doses are prescribed to different region depending on the risk of disease involvement

The gross disease (high risk) receives 70 Gy
Ipsilateral neck (intermediate risk) receives 60 Gy
Contralateral neck (low risk) receives 50 Gy



Conventional Planning

In conventional planning, this is often delivered as initial 50 Gy to all the areas followed to 2 boosts with reduced volumes, i.e.,
50 Gy/**2 Gy**/5 wks (low risk) → 10 Gy/**2 Gy**/1 wk (intermediate risk) → 10 Gy/**2 Gy**/1 wk (high risk)

Implications in H&N IMRT Regimen

IMRT Planning

A single plan with **differential dose per fraction** to areas of different risk on the same day

Thus 50 Gy to the low-risk areas are spread over 7 weeks instead over 5 weeks
Using Peters' approach, an additional 6 Gy would be required (3 Gy/wk x 2 wks)

By the same token, dose to intermediate risk area would need to be increased by 3 Gy (3 Gy/wk x 1 wk)

Many of the current H&N protocols typically prescribe prescribe **56 Gy**, **63 Gy**, **70 Gy** to low, intermediate, high risk PTVs

EQD2

For cases in which patients receive radiotherapy composed of **different fractionation scheme** or **modalities**, it is desirable to generate a **composite equivalent biological dose** in **2 Gy** fractions, known as **EQD2**

To equate a dose D given in dose d per fraction x n fractions to that given in 2 Gy per fraction,

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

$$\Downarrow$$

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

Example 1

What is the EQD2 of a treatment prescription of 72 Gy delivered in 2 Gy fractions?

Solution

EQD2 = 72 Gy

By definition, EQD2 is the biologically equivalent dose in **2 Gy fractions**. **EQD2** has also been referred to as the **NTD** (normalized total dose) or the **LQED** (linear quadratic equivalent dose).

Example 2

A treatment prescription of 72 Gy delivered in 2 Gy fractions is changed to deliver 3 Gy fractions, with the total dose adjusted accordingly so that the new prescription would be isoeffective with respect to late complications in a normal tissue characterized by an α/β ratio of 2 Gy.
If the α/β ratio for the tumor is 10 Gy, what is the tumor EQD2 of the new regimen?

Solution

To match **late effects**

$$\text{BED (2 Gy/fx)} = 36 \times 2 \times \left(1 + \frac{2}{2}\right) = 144\ \text{Gy}_2$$

$$\text{BED (3 Gy/fx)} = 144\ \text{Gy}_2 = \mathbf{n} \times 3 \times \left(1 + \frac{3}{2}\right) \rightarrow \mathbf{n} = 19 \rightarrow \text{Total dose} = 19 \times 3 = 57\ \text{Gy}$$

Example 2

Solution (Cont'd)

For **tumor dose**

BED (3Gy/fx) = $19 \times 3 \times \left(1 + \frac{3}{10}\right) = 74.1\ Gy_{10}$

To convert to 2 Gy/fx,

$74.1\ Gy_{10} = EQD2 \times \left(1 + \frac{2}{10}\right) \rightarrow EQD2 = 61.75\ Gy$

Alternatively,

$$EQD2 = D \times \frac{d + \alpha/\beta}{2 + \alpha/\beta} = 57 \times \frac{3 + 10}{2 + 10} = 61.75\ Gy$$

Example 3

Medical Residents Only

What is EQD2 of cervical cancer regimen given with external beam radiotherapy 45 Gy in 1.8 Gy per fraction followed by HDR brachytherapy 5.5Gy x 5 fractions?

For tumor dose, assume α/β of 10 Gy,

$$\textbf{EQD2 (tumor)} = 45 \times \frac{1.8 + 10}{2 + 10} + 27.5 \times \frac{5.5 + 10}{2 + 10} = 44.3 + 35.8 = \textbf{80 Gy}$$

For rectal dose, assume α/β of 3 Gy, and D_{2cc} of 3.5 Gy per fraction,

$$\textbf{EQD2 (Rectum)} = 45 \times \frac{1.8 + 3}{2 + 3} + 17.5 \frac{3.5 + 3}{2 + 3} = 43.2 + 22.8 = \textbf{66 Gy}$$

Final Words – The Axiom

Late Effects

Fraction size is the dominant factor in determining late effects; overall treatment time has little influence

Early Effects

Fraction size and overall treatment both determine the response of acutely responding tissue