JOINT MEETING

1ST ADVANCED AIRB COURSE IN RADIOBIOLOGY

BRESCIA MEETINGS IN RADIATION ONCOLOGY - 2015 EDITION

THE POWER OF BIOLOGY

Brescia – October 8th/9th, 2015

R. Santoni

"Numerologia" del modello lineare quadratico: teoria e pratica

Unità di Radioterapia
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Società Italiana di Radiobiologia

Fractionation: the linear-quadratic approach

Introduction:

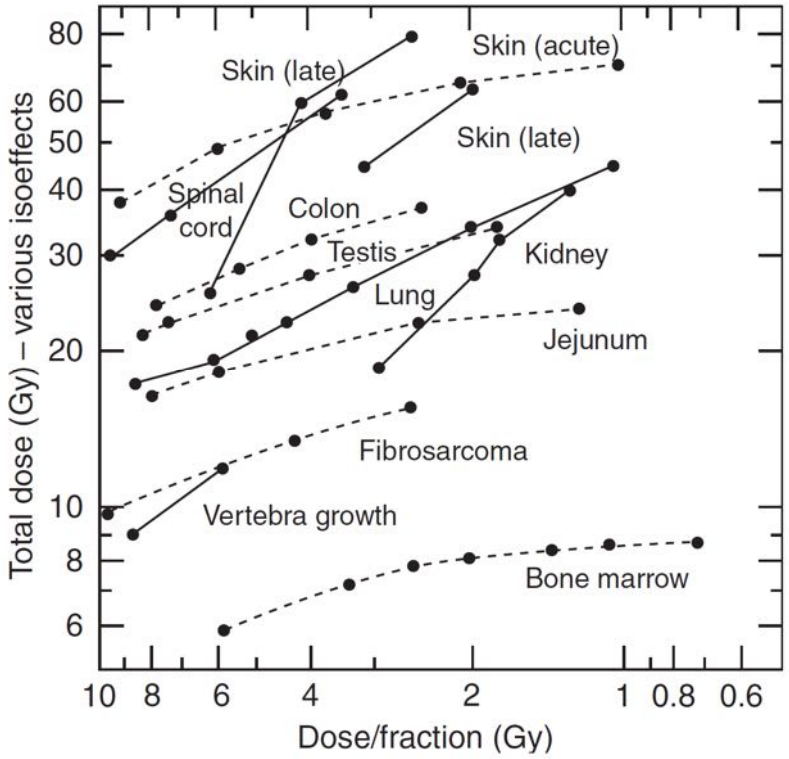
The relationships between total dose and dose per fraction for:

- late responding tissues
- acutely responding tissues
- tumours

provide the basic information required to optimize RT according to the dose per fraction and number of fractions.

The point is to obtain isoeffect curves for various normal tissues (Thames 1982)

Fractionation: the linear-quadratic approach



Thames et al. (1982)

Isoeffect curves for various normal tissues

Isoeffective total dose increases more rapidly with decreasing dose per fraction for late effects than for acute effects

Using lower doses per fraction will tend to spare late reactions if the total dose is adjusted to keep the acute reactions constant.

Fractionation: the linear-quadratic approach

The linear-quadratic (LQ) cell survival model can be used to describe the relationship between total isoeffective dose and the dose per fraction in fractionated radiotherapy and form a **quantitative** environment for:

balance between acute and late reactions (and effect on the tumour) as dose per fraction and total dose are changed.

Fractionation: the linear-quadratic approach

Several, mathematically equivalent, methods have been devised for performing bioeffect calculations with the LQ model

BED: following lecture!

disadvantage of BED as a measure of treatment intensity is that it is numerically much greater than any prescribable radiation dose of fractionated radiotherapy which could, therefore, be difficult to relate to everyday clinical practice

the simplest method of comparing the effectiveness of schedules consisting of different total doses and doses per fraction is to convert each schedule into an equivalent schedule in 2-Gy fractions which would give the same biological effect – EQD_2

Fractionation: the linear-quadratic approach

BED
$D * [1 + d/(\alpha/\beta)]$

EQD_2
$D * [d + (\alpha/\beta)/2 + (\alpha/\beta)]$

BED	EQD_2
$50 * [1 + (2/4)] = 75$ Gy	$50 * (2 + 4)/(2+4) = 50{,}0$ Gy
$44 * [1 + (2{,}75/4)] = 74.8$ Gy	$44 * (2{,}75 + 4)/(2+4) = 49{,}5$ Gy
$42{,}5 * [1 + (2{,}6/4)] = 70{,}0$ Gy	$42{,}5 * (2{,}6 + 4)/(2+4) = 48{,}0$ Gy
$28{,}5 * [1 + (5{,}7/4)] = 69{,}0$ Gy	$28{,}5 * (5{,}7 + 4)/(2+4) = 46{,}0$ Gy
$30 * [1 + (6.0/4)] = 75{,}0$ Gy	$30 * (6.0 + 4)/(2+4) = 50{,}0$ Gy

Fractionation sensitivity of human normal tissues - **Early and late reactions**

Tissue/organ Endpoint	α/β (Gy)	95% CL (Gy)	Source
Early reactions		α/β estimates for human endpoints	
Skin			
Erythema	8.8	6.9; 11.6	Turesson and Thames (1989)
Erythema	12.3	1.8; 22.8	Bentzen *et al.* (1988)
Dry desquamation	8	N/A	Chogule and Supe (1993)
Desquamation	11.2	8.5; 17.6	Turesson and Thames (1989)
Oral mucosa			
Mucositis	9.3	5.8; 17.9	Denham *et al.* (1995)
Mucositis	15	-15; 45	Rezvani *et al.* (1991)
Mucositis	8	N/A	Chogule and Supe (1993)
Late reactions			
Skin/vasculature			
Telangiectasia	2.8	1.7; 3.8	Turesson and Thames (1989)
Telangiectasia	2.6	2.2; 3.3	Bentzen *et al.* (1990)
Telangiectasia	2.8	0.1; 8.1	Bentzen and Overgaard (1991)
Subcutis			
Fibrosis	1.7	0.6; 2.6	Bentzen and Overgaard (1991)

Fractionation sensitivity of human normal tissues - **Late reactions**

Tissue/organ Endpoint	α/β (Gy)	95% CL (Gy)	Source
Late reactions		α/β estimates for human endpoints	
Breast			
Cosmetic change in appearance	3.4	2.3; 4.5	START Trialists Group (2008)
Induration (fibrosis)	3.1	1.8; 4.4	Yarnold *et al.* (2005)
Muscle/vasculature/Cartilage			
Impaired shoulder movement	3.5	0.7; 6.2	Bentzen *et al.* (1989)
Nerve			
Brachial plexopathy	3.5	N/A	Olsen *et al.* (1990)
Brachial plexopathy	2	N/A	Powell *et al.* (1990)
Optic neuropathy	1.6	7; 10	Jiang *et al.* (1994)

Fractionation sensitivity of human normal tissues - **Late reactions**
Similar reactions – Similar α/β estimates for human endpoints

Breast			
Induration (fibrosis)	3.1	1.8; 4.4	Yarnold *et al.* (2005)
Muscle/vasculature/Cartilage			
Impaired shoulder Movement	3.5	0.7; 6.2	Bentzen *et al.* (1989)
Nerve			
Brachial plexopathy	3.5	N/A	Olsen *et al.* (1990)
Lung			
Lung fibrosis (radiological)	3.1	0.2; 8.5	Dubray *et al.* (1995)
Head and neck			
Various late effects	3.5	1.1; 5.9	Rezvani *et al.* (1991)

Fractionation sensitivity of human tumours

Tissue/organ Endpoint	**α/β (Gy)**	**95% CL (Gy)**	**Source**
		α/β estimates for human endpoints	
Head and neck Tumours			
Larynx	14.5*	4.9; 24	Rezvani *et al.* (1993)
Vocal cord 1	~3	'wide'	Robertson *et al.* (1993)
Buccal mucosa	6.6	2.9	Maciejewski *et al.* (1989)
Tonsil	7.2	3.6;	Maciejewski *et al.* (1989)
Nasopharynx	16	-11; 43	Lee *et al.* (1995)
Other Tumours			
Skin	8.5*	4.5; 11.3	Trott *et al.* (1984)
Prostate	1.1	-3.3; 5.6	Bentzen and Ritter (2005)
Breast	4.6	1.1; 8.1	START Trialists Group (2008)
Oesophagus	4.9	1.5; 17	Geh *et al.* (2006)
Melanoma	0.6	1.1; 2.5	Bentzen *et al.* (1989)
Liposarcoma	0.4	1.4; 5.4	Thames and Suit (1986)

Fractionation sensitivity of human and experimental animals: normal tissues

Tissue/organ Endpoint	α/β (Gy)	Source
		α/β estimates experimental animals
Skin		
Desquamation	9.1–12.5	Douglas and Fowler (1976)
		α/β estimates for human endpoints
Desquamation	11.2	
	8.5; 17.6	Turesson and Thames (1989)
		α/β estimates experimental animals
Spinal cord		
Cervical	1.8–2.7	van der Kogel (1979)
Cervical	1.6–1.9	White and Hornsey (1978)
Cervical	2.2–3.0	Thames *et al.* (1988)
		α/β estimates for human endpoints
Myelopathy	3.3	Dische *et al.* (1981)

Linear-quadratic approach in clinical practice:

CHANGING THE DOSE PER FRACTION

Linear-quadratic approach in clinical practice:

CHANGING THE DOSE PER FRACTION - A simple example

Question: Which is the isoeffective dose in 2-Gy/fraction for spinal cord

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

A patient with metastatic bone pain located to a thoracic vertebra is considered for palliative radiotherapy using 4 x 5 Gy.

$$EQD2 = 20\ Gy\ \frac{5Gy + 2Gy}{2\ Gy + 2Gy} = 35\ Gy$$

$$EQD2 = 20\ Gy \times \frac{5Gy + 1.6Gy}{2\ Gy + 1.6Gy} = 36\ Gy$$

$$EQD2 = 20\ Gy\ \frac{5Gy + 3Gy}{2\ Gy + 3Gy} = 32\ Gy$$

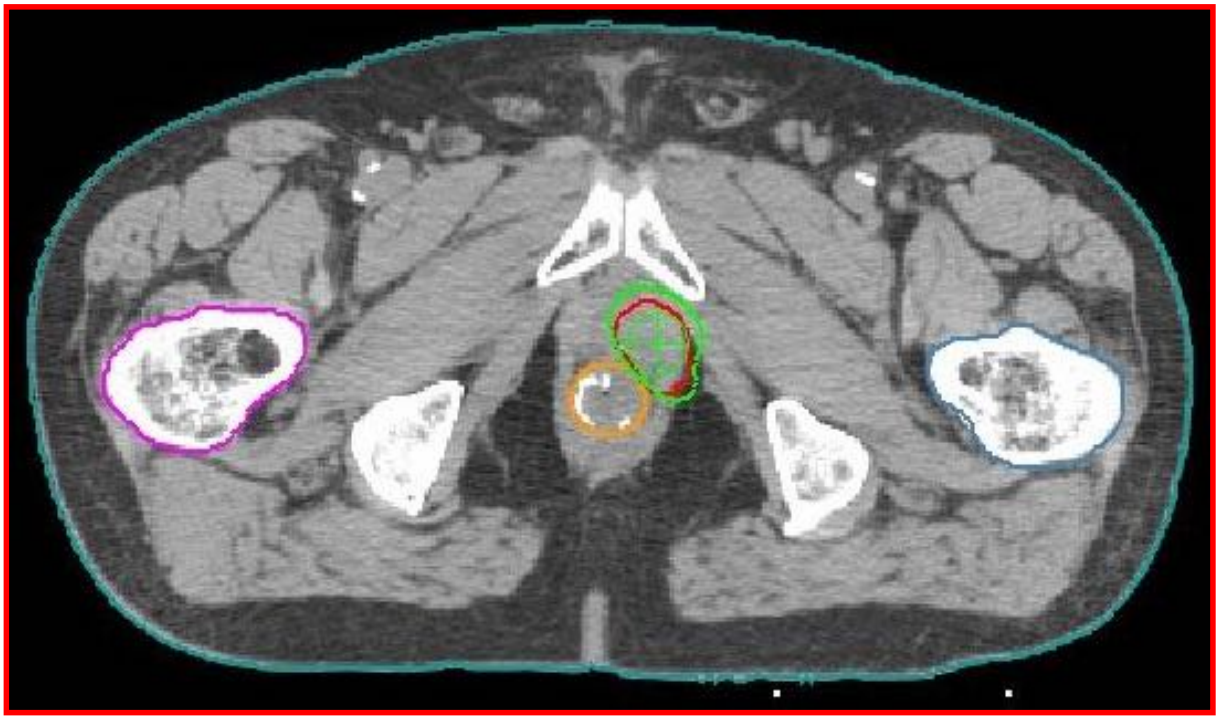
Spinal cord		
Cervical	1.8–2.7	van der Kogel (1979)
Cervical	1.6–1.9	White and Hornsey (1978)
Cervical	2.2–3.0	Thames *et al.* (1988)
Myelopathy	3.3	Dische *et al.* (1981)

α/β estimates experimental animals

α/β estimates for human endpoints

Linear-quadratic approach in clinical practice:

CHANGING THE DOSE PER FRACTION - The case of the prostate



Linear-quadratic approach in clinical practice:

CHANGING THE DOSE PER FRACTION - The case of the prostate

Tumor: α/β 1.5

$$EQD2 = D * \frac{d + (\alpha/\beta)}{2 + (\alpha/\beta)}$$

α/β estimates for human endpoints

$$EQD2 = 60\ Gy \quad \frac{3Gy + 1.5\ Gy}{2\ Gy + 1.5\ Gy} = 77\ Gy$$

$$EQD2 = 45\ Gy \quad \frac{4.5Gy + 1.5\ Gy}{2\ Gy + 1.5\ Gy} = 77\ Gy$$

$$EQD2 = 35\ Gy \quad \frac{7Gy + 1.5\ Gy}{2\ Gy + 1.5\ Gy} = 85\ Gy$$

Normal tissue α/β 3

$$EQD2 = 60\ Gy \quad \frac{3Gy + 3\ Gy}{2\ Gy + 3\ Gy} = 72\ Gy$$

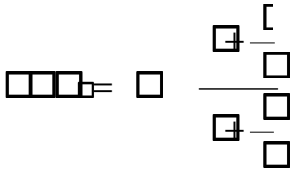
$$EQD2 = 45\ Gy \quad \frac{4.5Gy + 3\ Gy}{2\ Gy + 3\ Gy} = 67\ Gy$$

$$EQD2 = 35\ Gy \quad \frac{7Gy + 3\ Gy}{2\ Gy + 3\ Gy} = 70\ Gy$$

Linear-quadratic approach in clinical practice:

CHANGING THE DOSE PER FRACTION - The case of brain metastasis

A patient with brain metastasis considered for radiotherapy using 5 x 8 Gy or 1 x 20Gy.



D total dose
d dose per fraction

OARs	α/β (Gy)	Dose Constraints (Gy) 2Gy/fr	Dose Constraints (Gy) 8Gy/5fr 0 40 Gy	Dose Constraints (Gy) 20Gy/1fr = 20 Gy
Eye	2.9 (1)	D_{max}<50(5)	D_{max}<23	D_{max}<11
Lens of the eye	1.2 (2)	D_{max}<6(5)	D_{max}<2	D_{max}<1
Optic nerve	1.6(1)	D_{max}<54(5)	D_{max}<20	D_{max}<9
Optic chiasm	1.6(3)	D_{max}<54(5)	D_{max}<20	D_{max}<9
Brainstem	2(4)	D_{max}<54(5)	D_{max}<22	D_{max}<10

(1) Jiang et al. (1994)
(2) Perez et al. (2008)
(3) Ove et al.(2000)
(4) Dische et al. (1981)
(5) Lee et al.(2008)

Linear-quadratic approach in clinical practice:

CHANGING THE OVERALL TREATMENT TIME

Linear-quadratic approach in clinical practice:

CHANGING THE OVERALL TREATMENT TIME

Values for the **dose recovered per day owing to proliferation (Dprolif)** from clinical studies

Endpoint	Dprolif (Gy/day)	(95% CL) (Gy/day)	Source
Early reactions			
Erythema	0.12	0.12; 0.22	Bentzen *et al.* (2001)
Mucositis	0.8	0.7; 1.1 12	Bentzen *et al.* (2001)
Pneumonitis	0.54	0.13; 0.95	Bentzen *et al.* (2000)
Tumours			
Head and neck			
Larynx	0.74	0.30;	Robertson *et al.* (1998)
Tonsils	0.73	30	Withers *et al.* (1995)
Various	0.8	0.5; 1.1	Robers *et al.* (1994)
Various	0.64	0.42; 0.86	Hendry *et al.* (1996)
Esophagus	0.59	0.18; 0.99	Geh *et al.* (2005)
Non-small cell lung cancer	0.45	N/A	Koukourakis *et al.* (1996)

Linear-quadratic approach in clinical practice:

CHANGING THE OVERALL TREATMENT TIME

time effect is quantified by Dprolif,which is the dose recovered per day due to proliferation

The Danish Head and Neck Cancer Group (DAHANCA) conducted a randomized controlled trial of 66–68Gy in 33–34 fractions randomizing between five and six fractions per week
Expected difference in biologically effective dose for HNSCC between the two arms of the trial

$EQD2,T = EQD2T - (T - t)\ D_{PROLIF}$

$EQD2,38 = 66\ Gy + [(45 - 38)\ days \times 0.7Gy/day] = 66Gy + 4.9Gy = 70.9Gy$

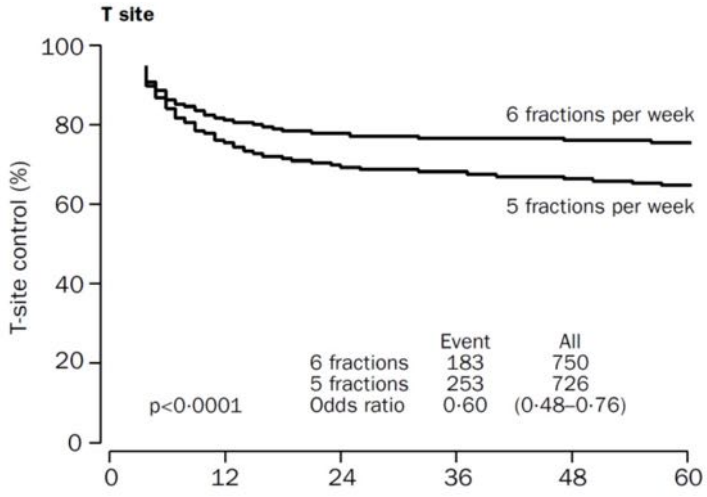
66Gy delivered over 38 days is biologically equivalent to 70.9Gy in 2-Gy fractions delivered over 45 day for HNSCC.

Effective 4.9-Gy dose increment

Linear-quadratic approach in clinical practice:

CHANGING THE OVERALL TREATMENT TIME

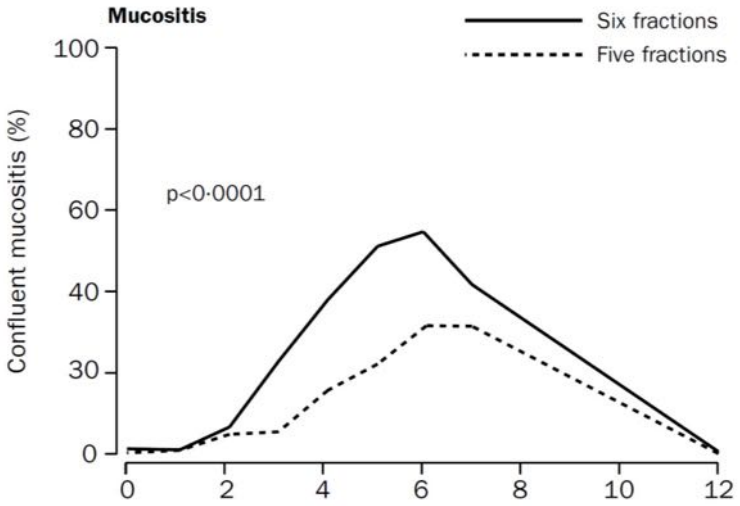
Six compared with five fractions per week improved:
tumour control (76% vs 64% for six and five fractions, p=0·0001)
preservation of the voice among patients with laryngeal cancer
(80 vs 68%, p=0·007).



Linear-quadratic approach in clinical practice:

CHANGING THE OVERALL TREATMENT TIME

Late radiation-induced morbidity was recorded in 1249 patients with at least 6 months of follow-up.
After 5 years of observation, the probability of developing a severe late reaction was less than 20%.



Linear-quadratic approach in clinical practice:

CHANGING IN FRACTION SIZE, GAP CORRECTION, α/β

Linear-quadratic approach in clinical practice:

CHANGING IN FRACTION SIZE, GAP CORRECTION

Preoperative radiotherapy with five times 5Gy from Monday to Friday; two fractions are given as planned no treatment could be given on Wednesday to finish as planned on Friday, delivering the isoeffective tumour dose by increasing the size of the two fractions to be given on Thursday and Friday is considered assuming α/β = 10Gy (tumor)

$$EQD2 = 15\ Gy \quad \frac{5Gy + 10Gy}{2Gy + 10Gy} = 18.75\ Gy$$

By simply dividing 18.75/2 we obtain 9.375 Gy. According to calculations it came out to be 6.7 Gy on Thursday and Friday.

How will this affect the risk of bowel damage?

Linear-quadratic approach in clinical practice:

CHANGING IN FRACTION SIZE, GAP CORRECTION

α/β of 4Gy - Bowel Various late effects

$$EQD2 = 10\ Gy * \frac{5Gy + 4Gy}{2Gy + 4Gy} + (2 \times 6.7\ Gy) * \frac{6.7Gy + 4Gy}{2\ Gy + 4Gy} = 38.9\ Gy$$

EQD2 for the 5Gy x 5 sessions corresponds to 37,5 Gy

How will this affect the risk of bowel damage?

EQD2 for the 6.7 x 4 sessions corresponds to 45.7 Gy

Would this fractionation affect bowel damage?

It may be questioned whether the use of the LQ model is safe anyway and reliable at these large doses per fraction! Probably NOT!

Linear-quadratic approach in clinical practice:

CHANGING IN FRACTION SIZE

α/β of 1.7Gy - Fibrosis

EQD2 = 25 Gy * $\frac{5Gy + 1.7Gy}{2Gy + 1.7Gy}$ = 45Gy

No increased risk of fibrosis between conventional (200*5, 4500cGY) and hypofractioanted (500*5, 2500cGY) regimens

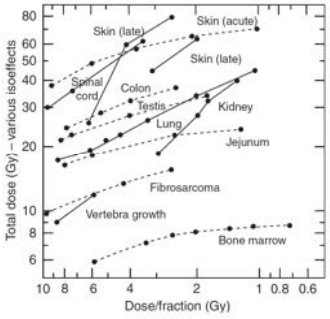
EQD2 = 26,8 Gy x $\frac{6.7Gy + 1.7Gy}{2Gy + 1.7Gy}$ = 60.8Gy

Considerably increased risk of fibrosis between conventional (200*5, 4500cGY) and hypofractioanted (6,7Gy*4, 2500cGY) regimens

This may make a difference!

Linear-quadratic approach in clinical practice:

CHANGING IN α/β



α/β of 1.7Gy – Fibrosis:

25 Gy in 5 x 5Gy sessions:
EQD2 45 Gy
28,6 Gy in 4 x 6,7 sessions without any time gap
EQD2 60.8 Gy

α/β of 4Gy – Bowel Various late effects:

25 Gy in 5 x 5Gy sessions:
EQD2 37,5 Gy
28,6 Gy in 4 x 6,7 sessions without any time gap
EQD2 45.7 Gy

α/β of 10Gy – Tumor:

25 Gy in 5 x 5Gy sessions:
EQD2 31.2 Gy
28,6 Gy in 4 x 6,7 sessions without any time gap
EQD2 33.5 Gy

This may make a difference!

Linear-quadratic approach in clinical practice:

HOT SPOT

Linear-quadratic approach in clinical practice:
HOT SPOT! Brachial plexus

The peak absorbed dose in the match zone between two abutted photon fields is measured to be 118 per cent of the dose on the central axis. A total dose of 50Gy is delivered in 25 fractions.
The peak physical absorbed dose per fraction in the match zone is 2.36Gy and the corresponding total dose is 25 * 2.36Gy 59.0Gy.

EQD2 = 59 Gy $\frac{2.36Gy + 3.5Gy}{2Gy + 3.5Gy}$ = 83 Gy

Late normal tissue endpoint

Brachial plexopathy 3.5

EQD2 = 59 Gy $\frac{2.36Gy + 10Gy}{2Gy + 10Gy}$ = 60.8 Gy

Tumor $\alpha/\beta = 10$

biological effect of a hot spot is important for the late endpoint

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 2, pp. 319–320, 2011

0360-3016/$ - see front matter

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doi:10.1016/j.ijrobp.2011.01.011

EDITORIAL

THE OMEGA ON ALPHA AND BETA

ELI GLATSTEIN, M.D.

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Over the years, I have told many trainees that one can be an excellent clinical radiation oncologist and not necessarily know squat about alpha/beta. I believe that remains true today.

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 4, pp. 1312–1314, 2012

0360-3016/$ - see front matter

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doi:10.1016/j.ijrobp.2011.12.045

EDITORIAL

WE FORGET AT OUR PERIL THE LESSONS BUILT INTO THE α/β MODEL

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It should be emphasized that the clinical application of LQ is not for generating absolute *ab initio* predictions of radiotherapeutic response, but rather to compare one fractionation/protraction protocol with another. When two fractionation schemes being compared each contain more than just a few fractions, their differences are expected to be dominated by repair and repopulation, and here the standard LQ model (6–8) would be expected to perform well. For comparative studies involving more "extreme" protocols, such as a single very high-dose fraction, the standard LQ model undoubtedly becomes less reliable

Linear-quadratic approach in the clinical practice: faith or skepticism?

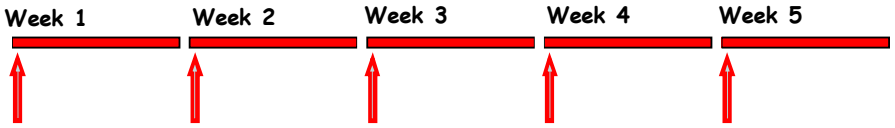
1. LQ model is the model of choice for bioeffect estimation in radiotherapy and can it is used in a wide range of calculations.

2. The dose range where the LQ model is supported by data is roughly 1 – 5Gy per fraction. Outside this range extreme caution is reccomended.

3. Clinical parameter estimates should be used whenever possible and animal values used with caution in applying results to the clinical situation.

4. In combined modality therapy, it may not be valid to use parameters derived from studies using radiation alone.

5. What to do in cases such this one? I really do not know!



Most of the material reported in this presentation is much better described in this fondamental book of Radiobiology

The first three editions of this book were under the editorship of Gordon Steel, but in this new edition Gordon has passed the editing pen to his two senior co-teachers, who have both been involved in these international courses since their inception in 1990. We acknowledge and thank Gordon for his tremendous effort and expert stewardship over the first three editions, and we hope very much that, in this new edition, we have managed to maintain the high standard of content, presentation and accessibility that has always been an integral part of this project.