Some applications of the LQ model

- Using the LQ model to correct for errors
- Hypofractionation
  - *effect of α/β*
  - *effect of long treatment times*
- Balloon brachytherapy

Using the L-Q model to correct for errors

A SIMPLE α/β-INDEPENDENT METHOD TO DERIVE FULLY ISOEFFECTIVE SCHEDULES FOLLOWING CHANGES IN DOSE PER FRACTION

MICHAEL C. JOINER, M.A., PH.D.

Int. J. Radiat. Oncol. Phys. Biol., Vol. 58, No.3, pp. 871-875, 2004

The Mike Joiner method

- Joiner found that if several fractions are delivered at the wrong dose/fraction, you can derive a dose/fraction to use for the remainder of the course that will result in the planned BEDs being delivered to *all* tissues
  - *it is independent of the α/β of the tissue*

The Mike Joiner method: definitions

- The planned total dose is:

$$D_p \text{ Gy at } d_p \text{ Gy/fraction}$$

- The dose given erroneously is:

$$D_e \text{ Gy at } d_e \text{ Gy/fraction}$$

- The dose required to complete the course is:

$$D_c \text{ Gy at } d_c \text{ Gy/fraction in } N_c \text{ fractions}$$

The Joiner equations

$$D_c = D_p - D_e \quad i.e.\ total\ dose\ is\ unchanged$$

$$d_c = \frac{D_p d_p - D_e d_e}{D_p - D_e}$$

$$N_c = \frac{D_c}{d_c}$$

Example: single fraction > 50% below planned

Planned treatment: 42 Gy at 7 Gy/fraction

Given in error: 2 fractions of 3 Gy

Then the dose/fraction needed to complete the treatment is:

$$d_c = \frac{D_p d_p - D_e d_e}{D_p - D_e} = \frac{42 \times 7 - 6 \times 3}{42 - 6} = 7.67 Gy$$

Example (cont'd.)

- The extra dose required is:

$$D_c = 42 - 6 = 36 \text{ Gy}$$

- Hence the number of fractions required is:

$$N_c = 36/7.67 = 4.7$$

- Since we cannot deliver 0.7 of a fraction, complete the treatment with 5 fractions of 36/5 = 7.2 Gy/fraction
  - *always round out the number of fractions **up**, since increased fractionation spares normal tissues*

Example: single fraction > 50% above planned

- Planned treatment: 42 Gy at 7 Gy/fraction
- Given in error: 1 fraction of 11 Gy
- Then the dose/fraction needed to complete the treatment is:

$$d_c = \frac{D_p d_p - D_e d_e}{D_p - D_e} = \frac{42 \times 7 - 11 \times 11}{42 - 11} = 5.58 Gy$$

Example (cont'd.)

- The extra dose required is:

$$D_c = 42 - 11 = 31 \text{ Gy}$$

- Hence the number of fractions required is:

$$N_c = 31/5.58 = 5.55$$

- Since we cannot deliver 0.55 fractions, complete the treatment with 6 fractions to a total dose of 31 Gy i.e. at 31/6 = 5.17 Gy/fraction

Example: total dose delivered is > 20% below that planned

- Planned treatment: 42 Gy at 7 Gy/fraction
- Given in error: 30 Gy at 5 Gy/fraction
- Then the dose/fraction needed to complete the treatment is:

$$d_c = \frac{D_p d_p - D_e d_e}{D_p - D_e} = \frac{42 \times 7 - 30 \times 5}{42 - 30} = 12 Gy$$

Example (cont'd.)

- The extra dose required is:

$$D_c = 42 - 30 = 12 \text{ Gy}$$

- Hence the number of fractions required is:

$$N_c = 12/12 = 1$$

- Therefore deliver one extra fraction of 12 Gy

Additional benefit of the Joiner model

The solution is not only independent of α/β but it is also independent of any geometrical sparing of normal tissues

Demonstration: last Example

- In the last Example, (a) 42 Gy at 7 Gy/fraction was found to be equivalent to (b) 30 Gy at 5 Gy/fraction plus 12 Gy at 12 Gy/fraction
- The BEDs for late-reacting normal tissues (α/β = 3 Gy) are 140 for (a) and 140 for (b)
- With a geometrical sparing factor *f* = 0.8, these BEDs are 96 for (a) and 96 for (b)

Hypofractionation

One of the advantages of highly conformal teletherapy is that it ought to be possible to deliver higher doses/fraction without exceeding normal tissue tolerance

Example: Hypofractionation for prostate therapy

- If the α/β for prostate cancer is lower than that for late-reacting normal tissues, as has been suggested, the prostate cancer cells will repair sublethal damage better than the normal cells
  - *hypofractionation ought to be better than conventional fractionation*

Proposed protocols for prostate cancer (if α/β = 1.5 Gy): conservative treatments

Equivalent to 66 Gy at 2 Gy/fraction with constant BED for late reactions (α/β = 3 Gy)

Abbreviations: bNED = no biochemical evidence of disease; NTD = normalized total dose (in 2 Gy fractions)

No. Frs	Dose per Fr	Total dose (Gy)	NTD (Gy)	bNED (%)
33	2.00	66.00	66.0	51.6
25	2.43	60.77	68.3	58.5
20	2.83	56.60	70.2	64.4
15	3.42	51.37	72.3	69.9
10	4.44	44.37	75.3	77.1
5	6.76	33.81	79.8	85.5

With hypofractionation the bNED could be improved from 51.6% to 85.5%

Fowler, 2003

More aggressive treatments: equivalent to 72 Gy at 2 Gy/fraction

Again, the BED for late reactions is kept constant for each fractionation scheme

The bNED could be improved from 69.2% to 94.0%

No. Frs	Dose per Fr	Total dose (Gy)	NTD (Gy)	bNED (%)
36	2.00	72.00	72.0	69.2
25	2.58	64.51	75.2	77.0
20	3.00	60.00	77.1	81.0
15	3.62	54.35	79.5	85.2
10	4.69	46.85	82.8	89.6
5	7.12	35.58	87.6	94.0

Fowler, 2003

Highly aggressive treatments: equivalent to 78 Gy at 2 Gy/fraction

The bNED could be improved from 82.6% to 97.6%

No. Frs	Dose per Fr	Total dose (Gy)	NTD (Gy)	bNED (%)
39	2.00	78.00	78.0	82.6
25	2.73	68.13	82.2	88.9
20	3.16	63.28	84.3	91.2
15	3.82	57.23	86.9	93.5
10	4.92	49.23	90.3	95.7
5	7.46	37.29	95.4	97.6

Fowler, 2003

Fowler's conclusions

Hypofractionation will increase the therapeutic ratio between tumor control and late reactions, provided that the α/β ratio for prostate tumors is lower than that for complications

Fowler's conclusions

- *It is obvious that too-modest hypofractionation will not yield enough gain in cure rates to be detectable with a practical number of patients in a clinical trial*
- *Fewer than about 20 fractions will probably be necessary for a significant gain*

Fowler's conclusions (cont'd.)

- *We caution against the hasty adoption of extreme hypofractionation*
  - *using very small numbers of larger fractions, given in an unusually short overall time, would need proper Phase I testing of the toxic effect of shortening the overall treatment time*

My opinion

- We also need to be careful since there is some concern that the α/β for prostate cancer may not be low and, if this is true, hypofractionation might be devastating
- We must take into account the effect that the presence of any hypoxic cancer cells might have on the outcome since the α/β for hypoxic cells is higher

Potential effect of hypoxic cells

Because hypoxic cells would be expected to have a higher α/β compared to well-oxygenated cancer cells, they will best be treated with *hyperfractionation*, not hypofractionation

Potential effects of long treatment times with IMRT for prostate cancer

- Because of the potentially low α/β for prostate cancer, there is some concern that longer treatment times associated with the delivery of IMRT might allow prostate cancer cells to repair more during each session of treatment than normal tissue cells
  - *this might be a problem for other cancers if late-responding normal tissue cells repair slower than tumor cells*

Potential effects of long treatment times for prostate treatments

IMPACT OF PROLONGED FRACTION DELIVERY TIMES ON TUMOR CONTROL: A NOTE OF CAUTION FOR INTENSITY-MODULATED RADIATION THERAPY (IMRT)

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The prescription dose was 81 Gy in 1.8 Gy fractions

Except where explicitly noted otherwise, the following LQ parameters were used in this study:

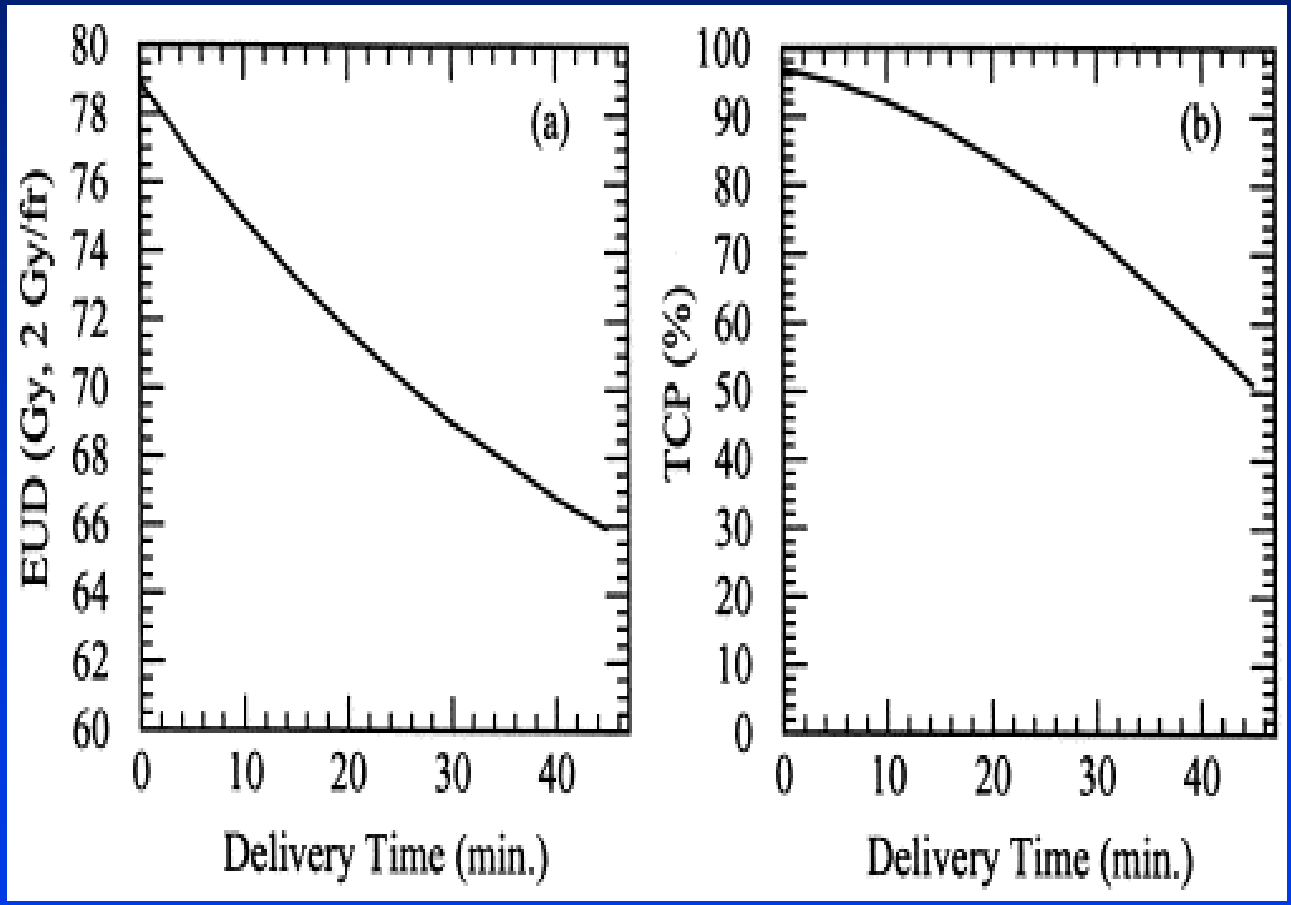
$\alpha = 0.15\ Gy^{-1}$, $\alpha/\beta = 3.1$ Gy, repair half time = 16 min

Int. J. Radiation Oncology Biol. Phys., Vol. 57, No. 2, pp. 543–552, 2003

EUD and TCP as a function of IMRT fraction delivery time

Extending the delivery time from 10 min to 30 min might decrease the EUD by about 5 Gy

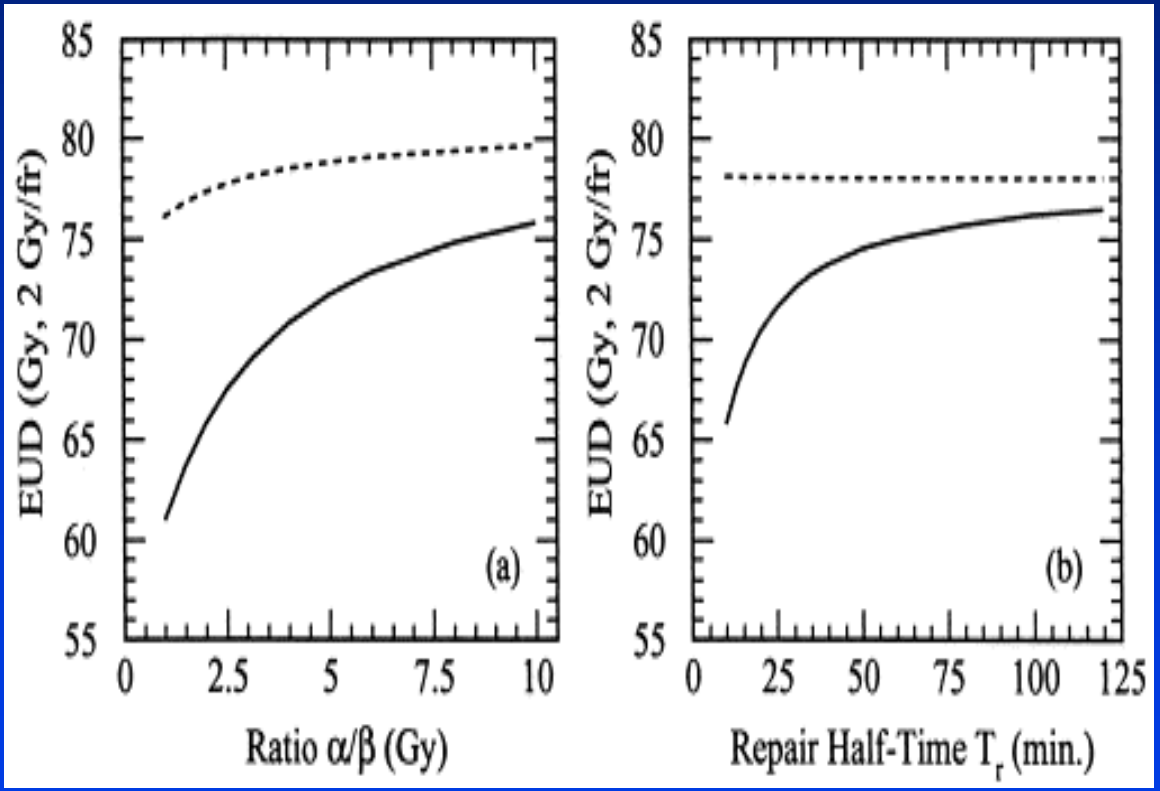
This might decrease the TCP by about 15%



Wang, et al (2003)

EUD as a function of α/β ratio and repair half-time for prostate cancer

--- 2 min. delivery time
— 30 min. delivery time



Wang, et al (2003)

Wang et al conclusions

- *Our calculations indicate that fraction delivery times in the range of 15 - 45 min may significantly decrease cell killing*
- *The total time to deliver a single fraction may have a significant impact on IMRT treatment outcome for tumors with a low α/β ratio and a short repair half-time*

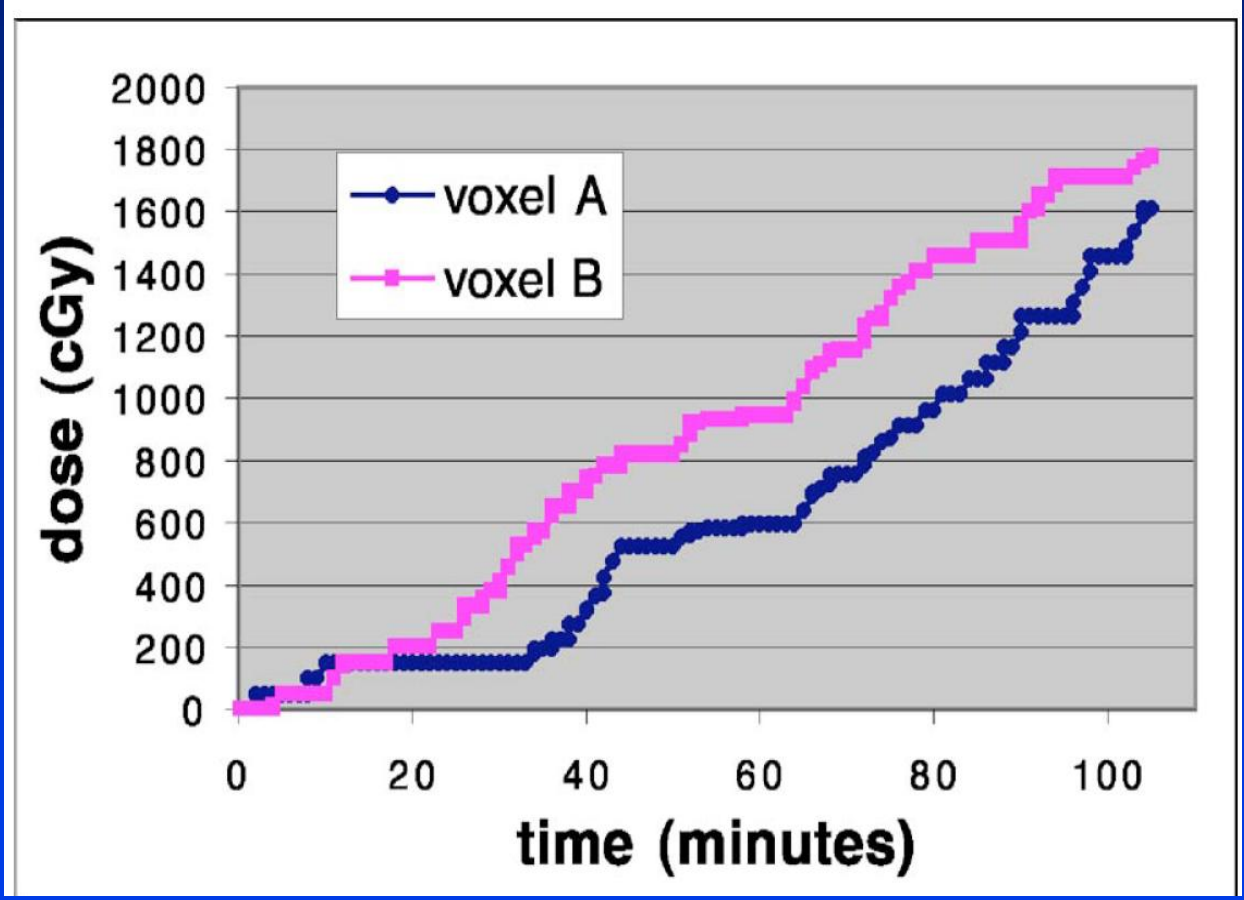
Wang, et al (2003)

CyberKnife treatments

- With the CyberKnife, treatment sessions can be as long as an hour-or-so
- This is the same order of magnitude as half times for repair, so the time to irradiate each specific voxel of tissue will affect the outcome in that voxel

Build up of dose for two sample voxels for a lung tumor treated by the CyberKnife

The dose in voxel A builds up slower than that in voxel B



Murphy, et al (2007)

Spatial distribution of the build up of dose

For the bottom right hand corner of the tumor (red) there is a >20 minute period during which it is not being irradiated

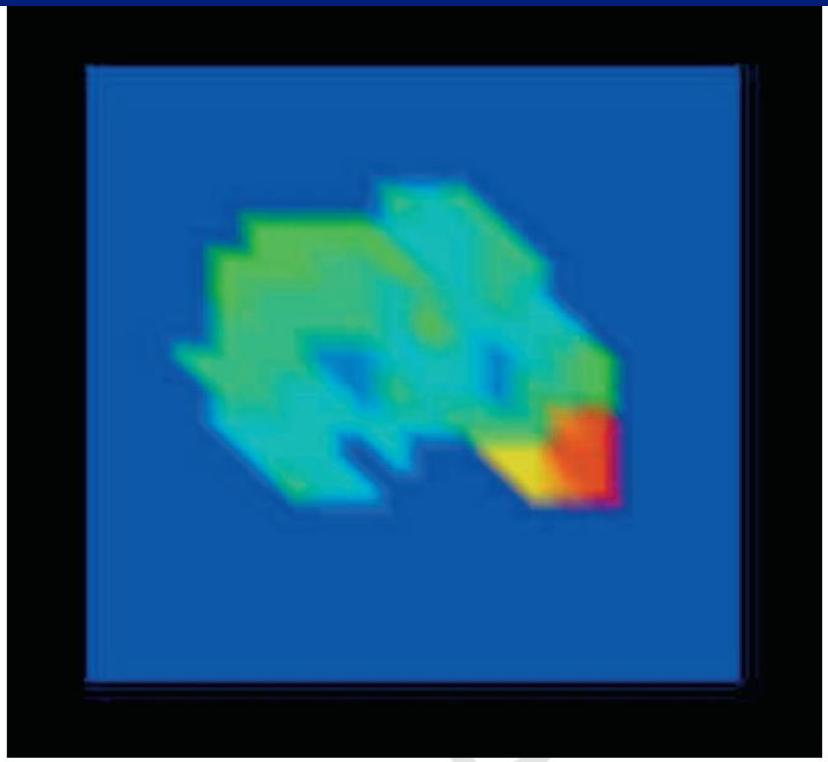


FIG. 2. The spatial distribution of longest significant (>5 min) pauses in the buildup of dose within the tumor volume. The color scale runs from <4 min (blue) to >20 min (red) in 5 min color increments.

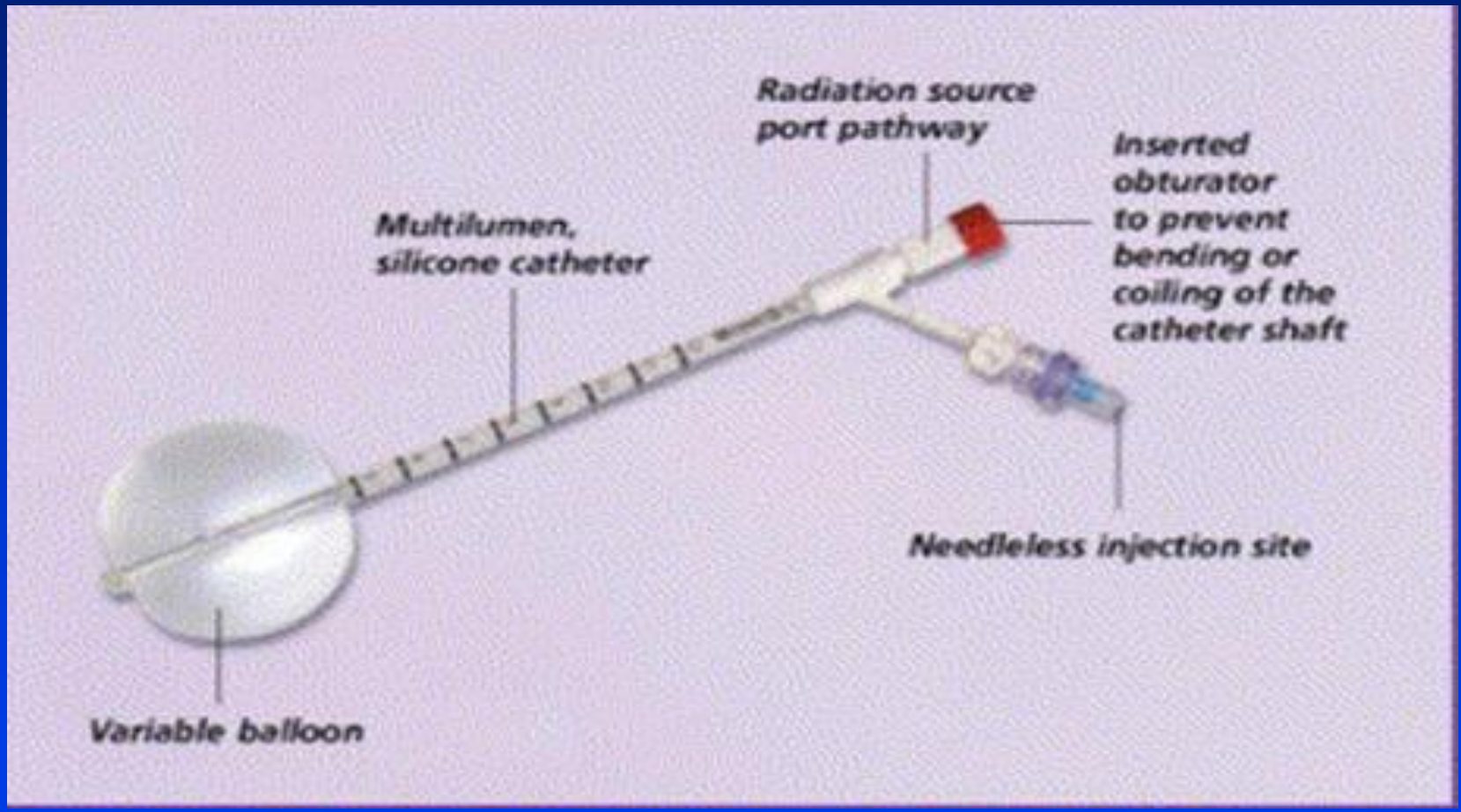
Murphy, et al (2007)

Authors' conclusions

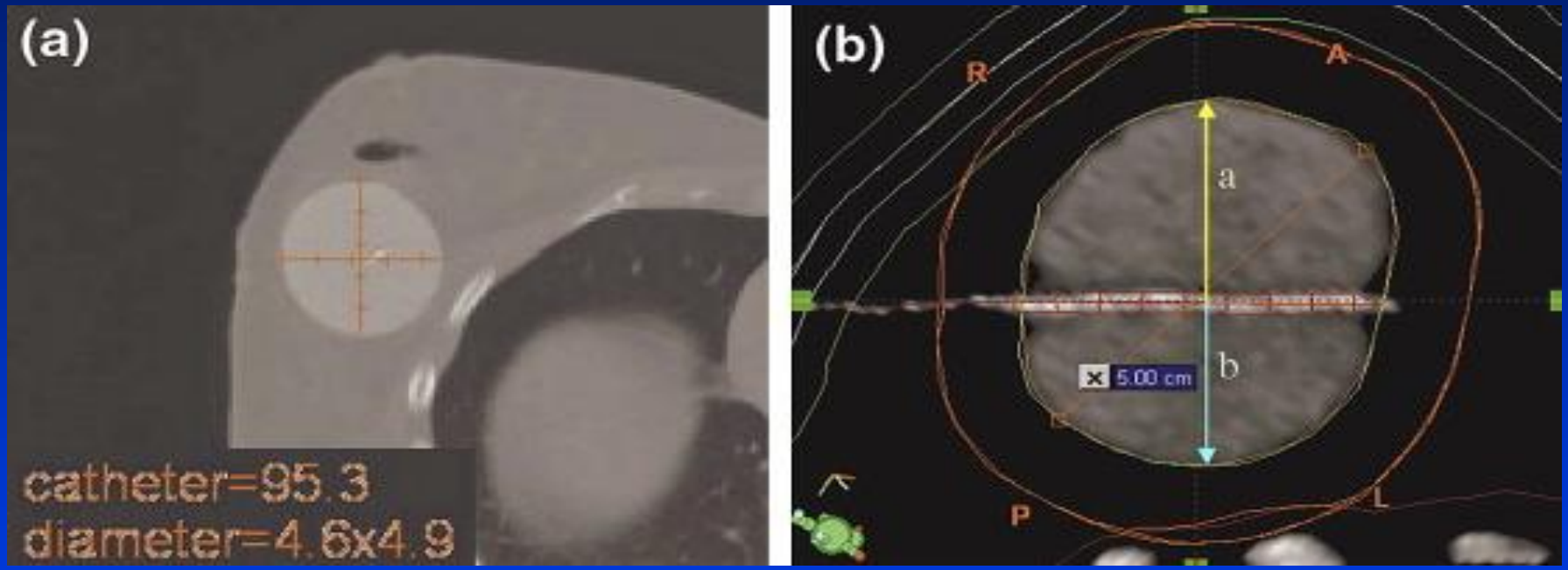
Our very simple model for repair as a function of dose delivery timing suggests that the intra-fraction timing of our sample treatment plan might reduce the effectiveness in some voxels by up to 15%

Murphy, et al (2007)

Partial breast irradiation by balloon brachytherapy



HDR balloon brachytherapy



The dose distribution around the cavity is concentric with and the same shape as the cavity. Doses are specified at 1 cm outside the balloon's surface

IJROBP, Vol. 60, No. 5, pp. 1393–1404, 2004

BIOLOGIC COMPARISON OF PARTIAL BREAST IRRADIATION PROTOCOLS

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"The BED values of (these) protocols resulted in tumor control BEDs roughly equivalent to a 50-Gy standard treatment, but consistently lower than the BEDs for regimens in which the tumor bed receives a total dose of either 60 Gy or 66 Gy"

Conclusions from this paper

"Therefore, it may be anticipated that the tumor control rates… may be lower for (these) regimens compared with standard whole breast RT using an additional boost dose to the tumor bed"

HDR balloon brachytherapy: Objective

Use the LQ model to demonstrate that this conclusion that HDR balloon brachytherapy of 3.4 Gy in 10 fractions should be less effective for tumor control than conventional teletherapy was wrong

Assumptions made in that study

- Uniform density of tumor cells throughout PTV
- All tumor cells receive dose of 3.4 Gy/fraction
- Linear-quadratic model with:
  - *tumor α = 0.3 Gy^{-1} and α/β = 4 or 10 Gy*
  - *T_{pot} = 13 days*
  - *kick-in time (T_k) for accelerated repopulation = 14 days*

The BED equation with repopulation

$$BED = Nd\left(1 + \frac{d}{\alpha/\beta}\right) - \frac{0.693T}{\alpha T_{pot}}$$

where:

T is the overall treatment time (in days)

T_{pot} is the potential doubling time of the cells (in days)

Alternative form of the BED equation with repopulation

- Some believe that there is a delay between the start of treatment and the onset of "accelerated repopulation"
- If T_k days is the "kick-in" time for accelerated repopulation, the LQ equation becomes:

$$BED = Nd\left(1+\frac{d}{\alpha/\beta}\right)-\frac{0.693(T-T_k)}{\alpha T_{pot}}$$

where T_{pot} = infinity (i.e. no repopulation) for $T<T_k$

Typical values assumed for T_k

- Some believe that there is no "kick-in" time i.e. $T_k = 0$
- Those who believe that there *is* a "kick-in" time usually assume that T_k is either 7, 14, 21, or 28 days

Objective

To demonstrate that balloon brachytherapy with 10 fractions of 3.4 Gy *is* equivalent in terms of tumor control to 60 – 66 Gy with teletherapy at 2 Gy/fraction

Simple approach

- Assume that all the cancer cells receive the prescription dose of 3.4 Gy/fraction with the balloon and ignore repopulation
- Use α/β = 10 Gy (Note: a smaller value would benefit the higher dose/fraction balloon therapy)

Simple approach solution

Equating BEDs for equal tumor effect (α/β = 10 Gy) gives the equivalent number of 2 Gy fractions, N_{eq}:

$$BED = 34\left(1+\frac{3.4}{10}\right) = 2N_{eq}\left(1+\frac{2}{10}\right)$$

$$\rightarrow \; N_{eq} = 19.0$$

Simple approach: summary

The equivalent number of fractions at 2 Gy/fraction is 19.0

- *we expected 30 - 33, so current balloon brachytherapy appears far less effective*

Slightly more sophisticated approach

Assume that all the cancer cells receive the prescription dose of 3.4 Gy/fraction with the balloon but account for repopulation

Assumptions

- Because any tumor cells left behind in the cavity wall are likely to be well oxygenated and rapidly dividing, we will assume that T_{pot} is slightly less than average and that there is no lag time ($T_k = 0$):
  - $\alpha = 0.3\ Gy^{-1}$
  - $T_{pot} = 6$ days and $T_k = 0$ days

Solution

The equivalent number of fractions at 2 Gy/fraction is 23.4

- *we expected 30 - 33, so current balloon brachytherapy still appears far less effective*

More sophisticated approach

Account for repopulation *and* account for inverse square law fall off of dose from the balloon surface out to 1 cm away, where it reaches 3.4 Gy/fraction

Method

- Calculate the cell surviving fraction (*S*) using the L-Q model by integrating the effect throughout the CTV (0 – 1 cm from the balloon surface)
  - *equate this to the S calculated for the uniformly irradiated cells with the teletherapy treatments*

Solution: compared to 2 Gy/fraction teletherapy

Balloon radius	N_{eq}
2.0 cm	27.5
2.5 cm	27.3
3.0 cm	27.1

We expected 30 - 33, so current balloon brachytherapy still appears to be less effective than the 2 Gy/fraction teletherapy treatments

Even more sophisticated approach

- Additionally account for gradually decreasing cancer cell density with distance from the cavity surface
- Assume that the density of cancer cells is a maximum at the balloon surface and falls linearly to zero at the distal edge of the CTV (at 1 cm away) and repeat integration throughout the CTV

Solution: compared to 2 Gy/fraction teletherapy

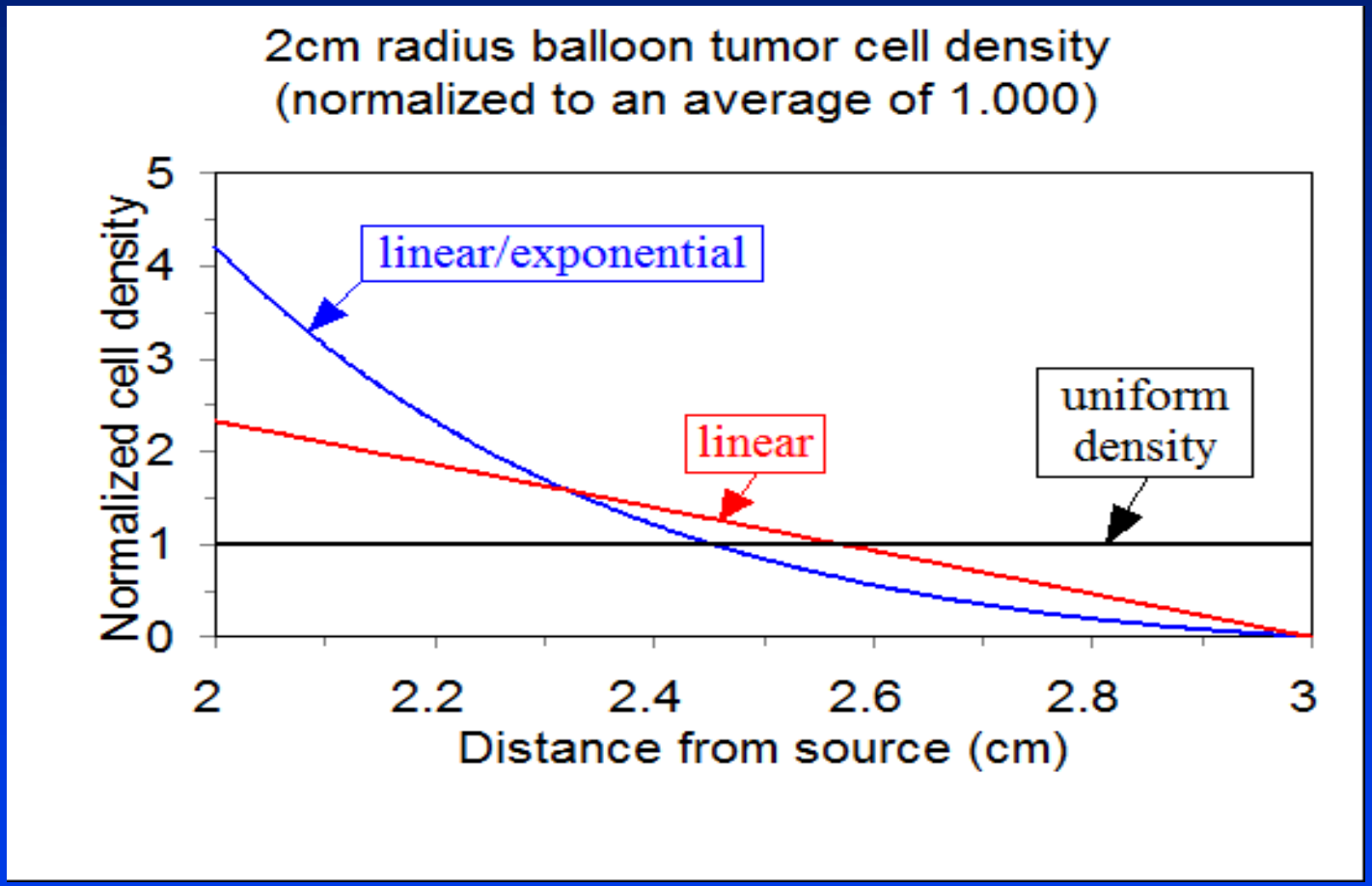
Balloon radius	N_{eq}
2.0 cm	30.9
2.5 cm	30.2
3.0 cm	29.9

We expected 30 - 33, so current balloon brachytherapy appears to be just about as effective as the 2 Gy/fraction teletherapy treatments

Most sophisticated approach

- Assume that tumor cell density decreases more rapidly than linearly as we get further from the cavity wall
  - *modify the linear decrease with an exponential factor (similar to a Poisson density distribution)*

The three tumor-cell density distributions



Solutions: compared to 2 Gy/fraction teletherapy

Balloon radius	N_{eq}
2.0 cm	32.6
2.5 cm	32.1
3.0 cm	31.7

We expected 30 - 33, so current balloon brachytherapy is clearly as effective as the 2 Gy/fraction teletherapy treatments

Conclusions

Despite warnings to the contrary, 3.4 Gy in 10 fractions with HDR balloon brachytherapy should be as effective in terms of tumor control as 30 – 33 fractions of teletherapy at 2 Gy/fraction

Warning!

Do not forget, the L-Q model is just an approximation