Radiobiological Models in Brachytherapy Planning and Evaluation

Zhe (Jay) Chen, PhD & David J. Carlson, PhD
Department of Therapeutic Radiology
Session at a Glance

• General introduction
  – Zhe (Jay) Chen, Ph.D.

• Basic concepts and relevant radiobiological models
  – David J. Carlson, Ph.D.

• Clinical applications in brachytherapy
  – Zhe (Jay) Chen, Ph.D.

• Questions & answers
  – David J. Carlson, Ph.D. & Zhe (Jay) Chen, Ph.D.

• Session ends promptly at 11:25 am
Rationale for this course

• Brachytherapy is just a little bit more complex than EBRT

  – Brachytherapy utilizes a multitude of radioactive sources & dose delivery techniques:

    ▪ Photon energies: 20 keV to 660 keV (e.g., $^{103}\text{Pd}$, $^{125}\text{I}$, $^{192}\text{Ir}$, $^{137}\text{Cs}$)
    ▪ Decay half-lives: ~10 days to 30 years (e.g., $^{131}\text{Cs}$, $^{137}\text{Cs}$)
    ▪ Temporary continuous LDR irradiation lasting hours to days (e.g., conventional intracavitary GYN)
    ▪ Permanent LDR irradiation with exponentially decaying dose rates (e.g., permanent interstitial implants for prostate and head & neck cancers)
    ▪ Multi-fraction HDR irradiations with different dose fractionations (e.g., intracavitary GYN/Cervix, interstitial prostate implant)

  – The spatial & temporal dose delivery patterns can be drastically different from one another and from EBRT

    ▪ Dose/dose rate can differ easily by a factor of 2 or more among techniques, or over the same target volume for a given technique
The clinical impact of such diverse spatial & temporal variations is difficult to assess using traditional dose-based metrics.

- The biological effects depend not only on the total dose given but also on how the dose is delivered.

  - *in vitro* Chinese Hamster cells
  - Breast cancer: EBRT (45 Gy) + $^{192}$Ir boost (37 Gy)

(Bedford et al., *Radiat Res*, 1973)

(Mazeron et al., *IJROBP* 1991)
Rationale for this course

- Radiobiological models can be a potentially useful tool for **relative comparison** of different spatial & temporal dose delivery patterns

  - Many models, purely empirical or based on high-level modeling of key cellular processes, have been developed

  - They are being used increasingly by medical physicists in comparing different treatment techniques and in deriving equivalent treatment regimes

- A good understanding of their potential, limitations, and intended use is critical for safe and beneficial use of the models in clinics

![Graph showing the number of peer reviewed publications returned by PubMed search using biologically effective dose and biologically effective dose + brachytherapy per year from 1988 to 2011. The graph indicates an increasing trend over the years.](image-url)
Goal & Objectives:

**Goal**: Review existing models and their use in selected brachytherapy modalities to facilitate meaningful and consistent use

**Objectives**: Help clinical medical physicists to

- Gain a better understanding of the rationale for using radiobiological models in brachytherapy treatment planning and evaluation
- Recognize the assumptions and limitations of the models and their intended use in relative comparison of competing brachytherapy modalities
- Be aware of the potential pitfalls regarding the selection, use, and interpretation of radiobiological models
Radiobiological Models in Brachytherapy Planning and Evaluation

Part I: Basic Concepts and Relevant Models

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Therapy Educational Course at the 55th Annual Meeting of the AAPM

Date and Time: August 8, 2013 from 10:30-11:25 AM
Location: Room 108
Conflict of interest: None
Biologically Guided Radiation Therapy (BGRT)

- Systematic method to derive prescription doses that integrate patient-specific information about tumor and normal tissue biology
- **Problem**: derived prescriptions may have large uncertainties
  - Uncertainties in physical and biological factors (experimental and clinical) that influence tumor and normal-tissue radiation response
  - Incomplete understanding of molecular and cellular mechanisms

- **Dose-Based TP** → *Physical objective functions*
  - Minimize dose gradients across tumor (uniformity), deliver prescribed isodose contours to target, minimize max. dose to critical structures, etc.
  - Uniform dose may not be most desirable

- **BGRT** → *Biological objective functions*
  - More direct approach to optimization instead of relying on dose-based surrogates
    - Maximize tumor cell killing (LQ) and tumor control probability (TCP)
    - Minimize normal tissue complication probability (NTCP)
Classical description of survival curves

- **Low doses**: shoulder region, survival falls slowly with dose
- **Intermediate doses**: region where survival curve bends and survival shows greater change with increasing dose
- **High doses**: region where survival falls rapidly with dose (curved? exponential?)

Most models used to fit survival curves are based this shape
  - Models based on target theory
    - Single target, single hit
    - Multi-target, single hit
    - Composite curves
  - Linear-quadratic (LQ) model
The double strand break (DSB)

- A DSB is formed when two breaks in the sugar-phosphate backbone occur on opposite sides of DNA helix within ~10 base pairs.

- Simple DSB:

- Many experiments for all types of DNA damage, including DSB, show that damage formation is proportional to absorbed dose up to hundreds of Gy.

**DSBs are formed through one-track mechanisms**

DSB induction in human fibroblasts (MRC-5) irradiated by 90 kVp x-rays (Rothkamm and Lobrich 2003)
One- and two-track radiation damage

Lethal lesions are created by the actions of one or two radiation tracks

1 track damage \( (\propto D) \)

2 track damage \( (\propto D^2) \)

Lethal DSB misrepair, unrepairable damage

Pairwise interaction of two DSBs
Exchange-type aberrations

Pairwise damage interaction (binary misrepair)

2 chromosomes:

1 chromosome:

DSB
Linear-quadratic (LQ) cell survival model

\[ S(D) = \exp \left[ -\left( \alpha D + \beta D^2 \right) \right] \]

\((\alpha D + \beta D^2)\) = expected number of lethal lesions per cell

\(\alpha\) = one-track lethal damage [Gy\(^{-1}\)]
\(\beta\) = two-track lethal damage [Gy\(^{-2}\)]

\(\alpha/\beta\) [Gy] is clinically used descriptor of intrinsic radiosensitivity
Tumor Control Probability (TCP) Model

TCP → relates tumor size and radiation dose to the prob. of tumor control (i.e., no tumor cells survive)

\[ TCP = \exp\left[-N \cdot S(D)\right] = \exp\left[-N \cdot \left(e^{-\alpha D - \beta D^2}\right)\right] \]

\( N = \text{initial # of tumor clonogens} \)

Tumor Control Probabilities for intermediate-risk prostate cancer patient group \((n = 40)\)
(Levegrun et al 2001)
Inter-patient variability in radiosensitivity

- Heterogeneity of human tumour radiation response is well known

- Many groups have accounted for variations in interpatient tumour heterogeneity by assuming that radiosensitivity values are normally distributed across the population

- If interpatient heterogeneity is ignored, TCP model generally results in an unrealistically steep dose-response curve

Factors that alter treatment effectiveness

4 R’s of Radiobiology give rise to “dose rate” effects:

- DNA repair
- Repopulation
- Reoxygenation & Redistribution

Treatment duration:
- mins → hours → days

Treatment effectiveness
Divide a tumor into voxels with radiosensitivity $\alpha_i$ and $\beta_i$. Correct SF for dose heterogeneity, inter- and intra-tumor variability in radiosensitivity and the R’s of radiobiology:

$$TCP = \prod_i TCP_i$$

$$TCP_i = \exp\left\{-N_0 f_i \exp\left[-D \left( \alpha_i + \beta_i G_i D_i \right) + \gamma_i T \right]\right\}$$

- **Oxygen and LET effects ($\alpha$ and $\beta$)**
- **Repair effects ($\mu$ or $\tau$)**
- $N_0 f_i$ is initial # of cells in the $i$th tissue region
- Repopulation rate in $i$th tissue region
DNA damage repair in the LQ model

\[ S(D) = \exp \left[ - \left( \alpha D + \beta G[\mu, t] D^2 \right) \right] \]

\( (\alpha D + \beta G[\mu, t] D^2) \) = expected number of lethal lesions per cell

\( \alpha = \) one-track lethal damage coefficient [Gy\(^{-1}\)]

\( \beta = \) two-track lethal damage coefficient [Gy\(^{-2}\)]

**G[\mu, t] is the Lea-Catcheside dose protraction factor**

\( \mu = \ln 2 / \tau = \) rate of DSB rejoining [h\(^{-1}\)]

**Limiting cases:**

\[ \lim_{t \to 0} G = 1 \quad \text{Instantaneous dose delivery} \]

\[ \lim_{t \to \infty} G = 0 \quad \text{Infinitely protracted dose} \]

General form of the protraction factor

Most general form of the protraction factor:

\[ G = \frac{2}{D^2} \int_{-\infty}^{\infty} dt \int_{-\infty}^{t} dt' D(t) D(t') \exp\{-\mu(t - t')\} \]

**Instantaneous absorbed dose rate (e.g., Gy/h) at time \( t \)**

Absorbed dose (Gy)

Probability per unit time sub-lethal damage (DSBs) is rejoined

**Probability per unit time sub-lethal damage (DSB) repair**

**Half-time for sub-lethal damage (DSB) repair**

For most mammalian cells, \( \tau \sim 0.1 \text{ h to } 10 \text{ h} \)
Dose rate effects and DNA damage repair

- Cell killing decreases with decreasing dose rate
- If $G(\mu,t)$ included, unique set of parameters can predict the data: $\alpha = 0.04$ Gy$^{-1}$, $\beta = 0.02$ Gy$^{-2}$, $\tau = 6.4$ h
- Repair of DNA damage occurs between fractions and during treatment delivery
- Effect increases with increase in delivery time

$\rightarrow$ **Critical for brachytherapy**

Biologically Effective Dose (BED)

- BED is an **LQ based** estimate of the *effective* biological dose that accounts for delivered **total dose**, the **dose fractionation**, and the **radiosensitivity** of tissue.
- Commonly used for isoeffect calculations.

Recall

\[ S(D) = \exp\left(-\alpha D - \beta GD^2 + \gamma T\right) \]

Take the negative logarithm of \( S \) and divide by \( \alpha \):

\[
BED \equiv \frac{-\ln S(D)}{\alpha} = D \left[ 1 + \frac{GD}{\alpha/\beta} \right] - \frac{\gamma T}{\alpha}
\]

- **Physical dose**
- **Relative effectiveness**
- **“Lost” dose due to repopulation effect**
Biologically Effective Dose (BED)

This expression is more general than the commonly used BED formalism

\[
\text{BED} = -\ln S(D) / \alpha = D \left[ 1 + \frac{GD}{\alpha / \beta} \right] - \frac{\gamma T}{\alpha}
\]

Repopulation effects are often neglected and \( G \) is set equal to \(-1/n\) (daily fractions), where \( n = \# \) of fractions.

\[
\text{BED} = D \left[ 1 + \frac{d}{\alpha / \beta} \right]
\]

where \( d = \) dose per fraction (Gy) and \( D = nd \)

Isoeffect Example for Prostate Cancer

- Assume $\alpha/\beta = 3$ Gy, for a standard EBRT fractionation of 39 fractions of 2 Gy:

$$\text{BED} = 78 \text{ Gy} \left[ 1 + \frac{2 \text{ Gy}}{3 \text{ Gy}} \right] = 130 \text{ Gy}$$

- Rearrange simplified BED equation:

$$d = \frac{\alpha}{\beta} \left( -n + \sqrt{n^2 + \frac{4n \times \text{BED}}{\alpha/\beta}} \right)$$

$$= \frac{3 \text{ Gy}}{2n} \left( -n + \sqrt{n^2 + \frac{4n \times 130 \text{ Gy}}{3 \text{ Gy}}} \right)$$
Isoeffect Example for Prostate Cancer

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![Graph showing isoeffect for different fractionation schemes]

King et al. (2009)  
Yeoh et al. (2006)  
Kupelian et al. (2005)

Standard Fractionation
General Isoeffect Calculations with BED

Two radiotherapy regimens are equally effective when

\[ \text{BED}_1 = \text{BED}_2 \]

\[
D_1 \left[ 1 + \frac{d_1}{\alpha / \beta} \right] = D_2 \left[ 1 + \frac{d_2}{\alpha / \beta} \right]
\]

\[ D_2 = D_1 \left[ \frac{d_1 + \alpha / \beta}{d_2 + \alpha / \beta} \right]
\]
Equivalent Dose in 2 Gy Fractions (EQD2)

- The total dose in 2-Gy fractions that would give the same log cell kill as the given schedule
- Often considered a more practical alternative than BED for the clinic
  - Familiar and intuitive quantity for physicians
  - Can be compared with clinical experience – decades of experience administering 2 Gy fractions

\[ \text{Equivalent dose in 2-Gy fractions} \rightarrow \text{EQD2} = D_1 \left[ \frac{d_1 + \alpha / \beta}{2 + \alpha / \beta} \right] \]

Fraction size (treatment 1)

\[ d_2 = 2 \text{ Gy} \]

Assumptions:
1. No change in treatment time
2. Repair negligible

- Note: also commonly written as
\[ \text{EQD2} = \frac{\text{BED}}{1 + 2 / (\alpha / \beta)} \]
• Brachytherapy dose distributions are inherently nonuniform

• An **Effective BED** can be calculated from individual BED$_i$ for all tumor subvolumes:

$$ \text{BED} = -\frac{1}{\alpha} \ln \left( \sum_i v_i e^{-\alpha \cdot \text{BED}_i} \right) $$

$v_i \equiv$ fractional volume receiving dose $D_i$ or initial dose rate $\dot{D}_{0i}$

• Information on 3D variation of BED over entire volume of clinical interest
• Evaluate and address biological significance of “hot” or “cold” dose regions
• Can be used to calculate and analyze BED-volume histograms

• **Note:** formulation above implicitly assumes that the (1) initial tumor burden and radiosensitivity are spatially uniform and that (2) RBE is unity
Equivalent Uniform Dose (EUD)

- EUD is defined as the uniform dose that, if delivered over the same number of fractions as the non-uniform dose distribution of interest, yields the same radiobiological effect
  - Assumes two dose distributions are equivalent if they cause same biological effect
  - Accounts for non-uniform dose throughout tissue of interest
- To extend the concept to normal tissues, Niemierko (1999) proposed a phenomenological formula referred to as the generalized EUD:

\[ gEUD = \left( \sum_{i} v_i D_i^a \right)^{1/a} \]

- \( v_i \) is the fractional organ volume receiving a dose \( D_i \)
- \( a \) is a tissue-specific parameter for volume effect

\( gEUD \) often used in plan optimization and evaluation because same model can be applied to both targets and OARs with a single biological parameter

Model assumptions and limitations

- **Limitations of the LQ model**
  - Does not explicitly capture many important biological factors, e.g., low dose hyper-radiosensitivity, bystander effects, possibility of other biological targets (e.g., endothelial cell apoptosis in vasculature)
  - High dose controversy (approximation for low dose rates and low doses, predictive up to ~10 Gy or higher?)

- **Uncertainties in radiosensitivity parameters**
  - Assumed values not meant to be interpreted as only biologically plausible parameters (inter- and intra-patient variability in radiosensitivity)
  - Lack of adequate data for many tumor sites and normal tissue

- **Best to practice evidence-based medicine**
  - Clinical data is the gold standard → must be skeptical of simplified models and understand limitations
  - Value of models highest in absence of good data → guide treatment decisions instead of relying on trial and error
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II. Clinical Applications and Discussions

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Date and Time: August 8, 2013 from 10:30-11:25 AM
Location: Room 108
Conflict of Interest: None
What are the models good for?

- Predicting absolute response – **No** (at least, not yet)
- Relative comparison – **Yes** (in most of the current applications)

Comparing the relative effectiveness of a given technique on different biological systems

- fast/slow growing tumors
- early/late reacting tissues
- aerobic/hypoxic cells
- impact of model parameters uncertainties
- ... 

Comparing the relative effectiveness of different treatment techniques on a given biological system

- $^{125}$I/$^{103}$Pd/$^{131}$Cs
- LDR/HDR/PDR
- impact of technique variation
- optimization of dose delivery techniques
- ...

(same dose/dose delivery pattern on different model parameters)

(different dose/dose delivery patterns on the same set of model parameters)
Protracted irradiation with constant dose rates

- Relevant clinical scenarios:
  - Intracavitary LDR brachytherapy using $^{137}$Cs source ($T_{1/2}$ of 30 yrs) for cervical cancer
    - e.g., total dose: 80 Gy to Point-A in two fractions
    - Dose rate at Point-A: ~ 0.53 Gy/hr, total treatment last 144 hrs
    - Dose rate: ~constant per fraction due to long $T_{1/2}$
  - Intracavitary HDR using $^{192}$Ir source ($T_{1/2}$ of 74 days) for GYN malignances, breast cancer, and interstitial HDR for prostate cancer, ...
    - Total dose: variable in multiple fractions
    - Dose rate at prescription point: ~ 12 – 50 Gy/hr, treatment last from minutes to < 1 hr per fraction
    - Dose rate: ~constant per fraction due to short treatment time

- How is the biological effectiveness of a prescribed dose affected by the rate of dose delivery?
Protraced irradiation with constant dose rate

- **The BED model**

\[
BED = D \left[ 1 + \frac{D}{(\alpha / \beta)} \frac{2}{(\mu T)^2} \left( e^{-\mu T} + \mu T - 1 \right) \right] - \frac{T - T_k}{\alpha} G(T) - \text{dose protraction factor}
\]

- **Recall the basic assumptions:**
  - Constant dose rate = \( D/T \)
  - For uniform dose distribution or dose at a point of interest
  - Radiobiological properties by five parameters (\( \alpha, \beta, \mu, \gamma, T_k \))
  - Mono-exponential repair kinetics
  - Uniform proliferation rate

- This model captures the influence of only 2 “R”s of radiobiology, i.e., repair & repopulation, on the dose rate effect

- In absence of these 2 “R”s, \( BED = D \left[ 1 + \frac{D}{(\alpha / \beta)} \right] \), no dose rate effect
The relative effectiveness of a given dose increases with increasing dose rate (repair half-time ($t_{1/2}$) = 1.5 hr, $\gamma = 0.0$, $D = 60$ Gy).

- The relative effectiveness of a given dose increases with increasing dose rate.
Single fraction LDR/HDR: Influence of dose rate - dependence on tissue type

\[ RE = 1 + \frac{D}{(\alpha / \beta)} \left( \frac{2}{(\mu T)^2} (e^{-\mu T} + \mu T - 1) \right) \]

- Altering dose rate has a greater influence on late-reacting (e.g., typical normal) tissues than for early reacting tissues (e.g. typical tumors)

\[ (t_{1/2} = 1.5 \text{ hr}, \gamma = 0.0, D = 60 \text{ Gy}) \]
Single fraction LDR/HDR: Influence of dose rate - impact on therapeutic gain

$RE = 1 + \frac{D}{(\alpha / \beta)} \frac{2}{(\mu T)^2} (e^{-\mu T} + \mu T - 1)$

Surrogate for potential therapeutic gain

$\frac{RE(\alpha/\beta = 10 \text{ Gy})}{RE(\alpha/\beta = 3 \text{ Gy})}$

$t_{1/2} = 1.5 \text{ hr}, \gamma = 0.0, D = 60 \text{ Gy}$

Consistent with the general philosophy favoring dose protraction while cautioning against using small number of high doses/dose rate

$t \to 0: (1 + 60/10)/(1 + 60/3) = 1/3$
The observations made so far are based on three key assumptions:

1) The $\alpha/\beta$ of tumor is greater than irradiated normal tissues
2) There is no cell proliferation
3) Normal tissues receives the same dose as the tumor

A change in these assumed conditions may lead to a different conclusion, for example

- The advantage of dose protraction on therapeutic gain diminishes for tumors with $\alpha/\beta \leq$ those of normal tissues (e.g., prostate Ca)

- Additional normal tissue sparing achievable in a HDR treatment could potentially improve the therapeutic ratio of the HDR technique to the level of LDR treatment
Multi-fraction HDR vs. LDR for cervix
- influence of normal tissue sparing

• An illustrative sample by Dale:
  - LDR reference treatment
    - 60 Gy in 72 hrs
    - $\alpha/\beta = 10$ Gy for tumor & 3 Gy for rectum, $t_{1/2} = 1.5$ hr, no repopulation
    - Rectum receive 80% of prescription dose ($f = 0.8$)

  \[
  \text{---} \quad \text{BED} = f \cdot D \left[1 + \frac{f \cdot D}{(\alpha / \beta)} \left(\frac{2}{(\mu_T)^2} (e^{-\mu_T} + \mu_T - 1)\right)\right]
  \]

  - $\text{BED}_{\text{tumor}}$ (LDR) = 81.0 Gy
  - $\text{BED}_{\text{rectum}}$ (LDR) = 92.8 Gy

  - HDR using 6 fractions with matching tumor BED
    \[
    \text{BED} = 6 \cdot f \cdot d \left[1 + \frac{f \cdot d}{(\alpha / \beta)}\right] = 81.0
    \]
    - $d = 7.6$ Gy ($f = 1.0$)
    - $\text{BED}_{\text{rectum}}$ = 111.6 Gy ($f = 0.8$)

  - Additional sparing needed to achieve LDR $\text{BED}_{\text{rectum}}$
    \[
    \text{BED} = 6 \cdot f \cdot d \left[1 + \frac{f \cdot d}{(\alpha / \beta)}\right] = 92.8
    \]
    - $f = 0.72$

• An extensive analysis by Brenner & Hall for fractionated HDR and LDR brachytherapy of the cervix also reached a similar conclusion

  Dale RG, *BJR* 63, 290-294; Brenner D, et al., 64, 133-141
Permanent interstitial brachytherapy (PIB)
- Protracted irradiation with declining dose rate

- For example, PIB for early-stage prostate cancer

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Energy (keV)</th>
<th>HVL (mm Pb)</th>
<th>Half-Life (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{125}$I</td>
<td>28.5</td>
<td>~0.03</td>
<td>60</td>
</tr>
<tr>
<td>$^{103}$Pd</td>
<td>21</td>
<td>~0.01</td>
<td>17</td>
</tr>
<tr>
<td>$^{131}$Cs</td>
<td>30.4</td>
<td>~0.03</td>
<td>9.7</td>
</tr>
</tbody>
</table>

- With unique dose delivery patterns
BED for PIB: The Dale Formalism

- Recall the equation: 
  \[ \text{BED} = D(T_{\text{eff}}) \cdot RE(T_{\text{eff}}) - \frac{\ln 2 \cdot (T_{\text{eff}} - T_k)}{\alpha T_d} \]

\[ RE(T) = 1 + \frac{D(T)}{(\alpha / \beta)} \times \frac{\lambda}{\mu - \lambda} \left( 1 - e^{-\lambda T} \right)^2 \left\{ \frac{1}{2\lambda} (1 - e^{-2\lambda T}) - \frac{1}{\lambda + \mu} (1 - e^{-(\mu + \lambda)T}) \right\} \]

\text{G(T)} – dose protraction factor

- It captures the interacting effects of changing dose rate during dose delivery with sublethal damage repair and cell repopulation

**Basic assumptions:**

- For uniform dose distribution or dose at a point of interest
- Radiobiological properties by five parameters (\(\alpha, \beta, \mu, \gamma, T_k\))
- Mono-exponential repair kinetics
- Uniform proliferation rate
- BED evaluated at the “effective treatment time”, \(T_{\text{eff}}\), is adequately representative of biological effects produced by the implant

(Dale RG, *BJR* 62, 241-244, 1989; & 58, 515-528, 1985)
BED for PIB: The Dale Formalism

- Definition of “effective treatment time”, $T_{eff}$

- In absence of cell proliferation:
  \[ \text{BED} \bigg|_{T=\infty} = D \times \left\{ 1 + \frac{\lambda}{\lambda + \mu} \frac{D}{\alpha / \beta} \right\} \]

- In presence of cell proliferation:
  - BED becomes negative at $T = \infty$
  - $A T_{eff}$ is defined as the time at which the rate of cell kill equal the rate of cell repopulation

\[ T_{eff} = T_{avg} \ln \left( \alpha D \frac{T_d}{T_{1/2}} \right) \]

$(^{125}\text{I}, D=145 \text{ Gy}, t_{1/2}=0.27 \text{ hr}, \alpha=0.15 \text{ Gy}^{-1}, \alpha/\beta=3\text{ Gy}, T_k=0)$

Yale SCHOOL OF MEDICINE
PIB for prostate cancer: Influence of radioactive source

- For monotherapy, the prescribed dose for different sources are usually different
  - Why using different doses? Are they biologically equivalent?

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>&lt;Energy&gt; (keV)</th>
<th>Half-Life (day)</th>
<th>Total Dose (Gy)</th>
<th>Initial DR (cGy/h)</th>
<th>$T_{\text{eff}}$ (day)</th>
<th>BED (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{125}\text{I}$</td>
<td>28.5</td>
<td>60</td>
<td>145</td>
<td>7</td>
<td>236</td>
<td>111</td>
</tr>
<tr>
<td>$^{103}\text{Pd}$</td>
<td>21</td>
<td>17</td>
<td>125</td>
<td>21</td>
<td>94</td>
<td>115</td>
</tr>
<tr>
<td>$^{131}\text{Cs}$</td>
<td>30.4</td>
<td>9.7</td>
<td>120</td>
<td>36</td>
<td>61</td>
<td>117</td>
</tr>
</tbody>
</table>

- Let’s perform BED calculation using the AAPM TG-137 recommended parameter set ($\alpha=0.15$ Gy$^{-1}$, $\alpha/\beta=3$ Gy, $t_{1/2}=0.27$ hr, $T_d=42$ days, $T_k=0$)

- It seems the BEDs are reasonably similar for this particular set of radiobiological parameters
PIB for prostate cancer: Influence of radioactive source - dependence on tumor growth rate

- What happens if some tumors grow at different rates?

⇒ Relative effectiveness depends on tumor growth rate: $^{125}$I relative more effective for slow growing tumor, $^{103}$Pd and $^{131}$Cs are better for fast growing tumors
PIB for prostate cancer: Influence of radioactive source - interplay with treatment-induced temporal variations

- Is the source with shorter decay half-life always better in practice?
  - “Yes”, for static implants
  - “?”, when tumor/source position varies during treatment

- Severity & time-to-resolution vary widely from patient to patient
  (magnitude: 30 to 100%; resolution half-life: 4 to 25 days)*

- Edema forces the sources to deviate from their planned locations

- It can have a significant impact on the actual dose delivered to patient**

PIB for prostate cancer: Influence of radioactive source - interplay with procedure-induced prostate edema

- Edema-induced reduction in BED as a function of edema magnitude and resolution half-life for pre-planned prostate implant

⇒ Source with shorter decay half-life and lower photon energy is more sensitive to edema induced reduction in BED

BED for PIB: Concerns for *proliferating* tumors (?)

- Zaider et al. introduced an iso-effective dose (IED) formalism that is mathematically well behaved in the limit of \( t \rightarrow \infty \)

\[
IED(t) = -\frac{1}{\alpha} \log \left( \frac{S_0(t)e^{(b-d)t}}{1 + bS_0(t)e^{(b-d)t}} \int_0^t \frac{e^{(b-d)u}}{S_0(u)e^{(b-d)u}} \, du \right)
\]

- \( S_0(t) \): cell survival probability at time \( t \), in absence of cell proliferation
- \( b \): cell birth rate
- \( d \): spontaneous cell death rate
- \( b-d = \ln(2)/T_d \)

(Zaider M et al., *PMB*, 2000; **45**:279-293 & 2007; **52**:6355-6362)
BED vs. IED: Permanent prostate brachytherapy

• Impact on deriving iso-effective prescription dose for new sources:
  
  - e.g., using $^{125}$I implant with 145 Gy as a reference:
    
    | Radioactive Decay Half-life (day) |
    |----------------------------------|
    | 0  | 0.84 |
    | 10 | 0.86 |
    | 20 | 0.88 |
    | 30 | 0.90 |
    | 40 | 0.92 |
    | 50 | 0.94 |
    | 60 | 0.96 |
    | 70 | 0.98 |
    | 80 | 1.00 |
    | 90 | 1.02 |

    - BED model produces lower iso-effect prescription dose than IED model

    - The difference becomes greater for faster-growing tumors using source of shorter half-life
      
      - For $T_d = 42$ days: the difference is 2.7% & 3.5% lower for $^{103}$Pd and $^{131}$Cs, respectively
      - For $T_d = 5$ days: the difference is 8.4% & 13.4% lower for $^{103}$Pd and $^{131}$Cs, respectively

(Chen Z and Nath R, *IJROBP*, 2012; 84:S755)
Concluding Remarks

• “Essentially, all models are wrong, but some are useful”
  - 1987, George E.P. Box

• When used properly, radiobiological modeling in brachytherapy can provide a potentially useful tool for
  – performing efficient pre-clinical evaluation of the relative clinical effects of different dose delivery patterns
  – conducting meaningful comparison of the treatment outcomes of different techniques and their efficacy relative to EBRT
  – optimizing the treatment efficacy of brachytherapy in either mono-therapy or combined modality settings.
Thank You!