The Impact of Cobalt-60 Source Age on Biologically Effective Dose in Gamma Knife Thalamotomy

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Disclosures

- I have no conflicts of interest to disclose
Background

- Tremor greatly reduces QoL
  - Parkinsonian
  - Multiple Sclerosis
  - Essential
    - Incidence ~616 per 100,000 people

- Treatment options
  - Medical management
  - Surgical thalamotomy
  - RF ablation
  - DBS
  - Gamma Knife (GK) radiosurgery

GK Thalamotomy

- Single 4mm shot to the thalamic ventralis intermedius (VIM) nucleus to ~130 Gy*

GK Thalamotomy

- Promising efficacy
  - >80% tremor improvement in most series

- Toxicity rare (<10%), but can be severe
  - Hemiparesis, paresthesia, dysarthria, dysphagia, gait disturbance, death due to hemorrhage/necrosis
  - Multifactorial

Anecdotal reports: increased toxicity with Cobalt-60 source replacement

GK Thalamotomy Source Age / Dose Rate

Cobalt-60 lifespan (half-life ~5.25 years)

New source → Replacement → Old source

Source Activity ↓
Dose Rate ↓

Treatment Time ↑

↑ toxicity?
↓ efficacy?

Hypotheses

• Given high Rx dose of GK thalamotomy, biologically effective dose (BED) of treatment may vary significantly with Cobalt-60 source age

• This variation may substantial enough to expect effect on clinical outcome

• A BED model based on the linear-quadratic (LQ) model with correction for intra-fraction DNA repair could estimate BED variation with source age
Methods - BED: the LQ Model

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

“G” = protraction factor
(~intra-fraction repair)

\[ G = \frac{2(e^{-\lambda T} + \lambda T - 1)}{(\lambda T)^2} \]

T = irradiation time (~Co-60 source age)

\[ \lambda = \frac{\ln 2}{\tau} \]

\( \tau \) = DNA repair half-time
(~0.1 to 10 hr)

Adapted from Carlson et al.
GK Thalamotomy BED Model Construction

Model Parameters:

\( D, T, \alpha/\beta, \tau \)

- \( D \) Dose
- \( T \) Treatment time
- \( \alpha/\beta \) Alpha / Beta
- \( \tau \) DNA repair half-time

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

\[
G = \frac{2(e^{\lambda T} + \lambda T - 1)}{(\lambda T)^2}
\]

\[
\lambda = \frac{\ln 2}{\tau}
\]
Model Parameters:
- **Dose** = 130 Gy

- **Treatment time** ~ Co-60 Source Age
  - New Source: Dose Rate(t=0) = 2.99 Gy/min
  - Exponential activity decay ($T_{1/2} = 5.25$ years = 63 months)

\[
A = A_0 \times \exp \left[ -\ln(2) / 63 \times t \right]
\]

Dose Rate(t) = Dose Rate(0) x A

\[\text{Treatment time (T)} = \frac{\text{Rx Dose}}{\text{Dose Rate (t)}}\]

*derived from departmental/vendor data*
Model Assumptions:

- **α/β**
  - Empirical data suggests $\alpha/\beta \sim 2$ for CNS tissue

- **τ**
  - Bi-exponential DNA repair half-times ("fast" and "slow" components)
    - **Model range:** $\tau$(fast) = 0.1 to 0.7 h; $\tau$(slow) = 2 to 6 h
    - **"Most plausible" scenario:** $\tau$(fast) = 0.38 h; $\tau$(slow) = 4.1 h

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

\[G = \frac{2(e^{-\lambda T} + \lambda T - 1)}{(\lambda T)^2}\]

\[\lambda = \frac{\ln 2}{\tau}\]
Results

Change in Treatment Time (T) with Co-60 Source Age

Treatment Time
Old source: 88 min (1.48 Gy/min)
New source: 43 min (2.99 Gy/min)
Results

% Decrease in BED with Cobalt-60 source age for 130 Gy thalamotomy

With new source replacement:*

15.6% relative increase in BED (range: 11-20%)

*Using “most plausible” Tau assumptions. **with replacement after 63 months

[Graph showing % Decrease in BED with Cobalt-60 source age for 130 Gy thalamotomy with lines representing different Tau values: \( \tau_f = 0.7, \tau_s = 6 \), \( \tau_f = 0.38, \tau_s = 4.1 * \), \( \tau_f = 0.1, \tau_s = 2 \).]
Conclusions

• Using biologically “most plausible” assumptions, Cobalt-60 source replacement causes a relative BED increase of $\sim16\%$ for GK Thalamotomy, that then declines by $\sim3\%$ per year over Cobalt-60 lifespan
  – Magnitude of BED change dependent on DNA-repair kinetics, timing of source replacement, initial source activity

• Co-60 source age and dose rate should be considered in the study and use of GK thalamotomy and other high-dose GK treatments
Limitations / Next Steps

- Clinically correlated data needed
  - Toxicity vs. efficacy
  - Radiographic changes

- Practice changes?
  - Prescription dose adjustment with Co-60 source age
  - Prolong treatment time with selective collimation
Thank You

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Appendix

Factors affecting toxicity:
- Target placement
- Patient sensitivity
- Lesion size result
Results

Decrease in BED with increased treatment times 130 Gy thalamotomy

*Using “most plausible” Tau assumptions

Increase Rx dose $\rightarrow$ Increase %BED change

Increase starting dose rate, DECREASE %BED change

Increasing “Tau” $\rightarrow$ DECREASE %BED change

$\tau_f = .1, \tau_s = 2$

$\tau_f = .38, \tau_s = 4.1^*$

$\tau_f = .7, \tau_s = 6$
Model Assumptions:

- **α/β**
  - Empirical data suggests $\alpha/\beta \sim 2$ for CNS tissue

- **τ (DNA repair half-time)**
  - Empirical evidence suggest bi-exponential DNA repair half-times ("fast" and “slow” components)

<table>
<thead>
<tr>
<th>Rat Spinal Cord Study</th>
<th>Fast (hr)</th>
<th>Slow (hr)</th>
<th>% fast repair</th>
<th>a/b (gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K.K Ang, Radiotherapy and Oncology, 1992</td>
<td>0.7</td>
<td>3.8</td>
<td>38%</td>
<td>2</td>
</tr>
<tr>
<td>Pop et al, Radiotherapy and Oncology, 2000</td>
<td>0.19</td>
<td>2.16</td>
<td>51%</td>
<td>2.47</td>
</tr>
<tr>
<td>Landuyt et al, Radiotherapy and Oncology, 1997</td>
<td>0.25</td>
<td>6.4</td>
<td>50%</td>
<td>2</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td><strong>0.38</strong></td>
<td><strong>4.1</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Model range: $\tau$(fast) = 0.1 to 0.7 h; $\tau$(slow) = 2 to 6 h

- “Most plausible” scenario: $\tau$(fast) = 0.38 h; $\tau$(slow) = 4.1 h
  - With assumed equal contribution (50:50) in DNA repair
Dose rate effects and DNA damage repair

- Cell survival increases with decreasing dose rate

- If dose protraction effects included in the model, a unique set of parameters can predict the entire data set:
  - $\alpha = 0.04 \text{ Gy}^{-1}$
  - $\beta = 0.02 \text{ Gy}^{-2}$
  - $\tau = 6.4 \text{ h}$

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**

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

**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**
BED in the literature

This derived expression is more general than the commonly used BED formalism

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

In the literature, repopulation effects are usually neglected and \( G \) is set equal to \( 1/n \) (appropriate for daily fractions), where \( n = \text{number of fractions} \).

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

where \( d = \text{dose per fraction (Gy)} \) and \( D = \text{total treatment dose (= nd)} \).

Absolute Decrease in BED with Cobalt-60 source age for 130 Gy thalamotomy
Results

% Decrease in BED with Cobalt-60 source age for 130 Gy thalamotomy

-18.0%
-16.0%
-14.0%
-12.0%
-10.0%
-8.0%
-6.0%
-4.0%
-2.0%
0.0%

0 10 20 30 40 50 60 70

Cobalt-60 Source Age (months)

With new source replacement:

15.6% relative increase in BED

*Using “most plausible” Tau assumptions

τ_f = .7, τ_s = 6

τ_f = .38, τ_s = 4.1*

τ_f = .1, τ_s = 2