Clinical Applications of Brachytherapy Radiobiology

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Radiobiology is Essential

- Knowledge of radiobiological principles is essential to the brachytherapist
- Empirical prescription replaced by modelling
- Radiobiology no substitute for a badly placed implant—good geometry is still key
Dose volume differences

EBRT
Volume treated is usually quite large.
Variation in dose is kept minimal
Homogeneous dose distribution with < 5% lower doses and < 7% higher doses

BT
Treated Volume is rather small
Minimum dose is prescribed to an isodose encompassing the PTV
Very inhomogeneous dose distribution within the treated volume
Gynaecologic Brachytherapy

Repair

- The lower the dose rate of radiation, the more likely that repair will occur.
- PDR- allows time for sublethal damage repair during treatment.
- HDR- full normal tissue repair occurs if more than 6-24 hrs between fractions.
Repopulation

- Clear evidence of improved tumour control and survival if RT is given in shorter overall time (Perez 1995, Petereit 1995).
- Okkan et al 2003-average time to complete RT with HDR=70 days, with LDR=57 days.
- Chen et al 2003-DFS drops from 83% to 65% if overall RT time over 63 days (HDR).

Reoxygenation

- Clear evidence of decreased survival in cervix Ca with a low initial Hb/decreased Hb during treatment
- PDR-allows for acute hypoxia to correct during treatment.
- HDR-allows for tumor shrinkage and reoxygenation of chronically hypoxic areas.
Effect of Hypoxia on Radiosensitivity

\[
\text{OER} = \frac{\text{radiation dose in hypoxia}}{\text{radiation dose in air}}
\]

Steel, 2002

Reassortment

Cells can pass out of radioresistant late S and early G2 into more radiosensitive G2 and M during treatment.

Steel, 2002
Dose-fractionation

- How best to convert HDR to LDR?
- For cervix recommend HDR<7 Gy per fraction to achieve excellent cure with low late toxicity
- But in India 20 Gy in 2 fractions used with good effect
  - Av BED doses in US
    - IB & IIB-96 Gy_{10}
    - IIIB-100 Gy_{10}
  - Av BED doses in UK (historic)
    - 83.3 Gy_{10}
  - Av BED doses in Vienna
    - 100.7 Gy_{10}
Correlated with control!

HDR BT Cervix Ca

Importance of fraction size (to point A)

<table>
<thead>
<tr>
<th>Complications:</th>
<th>&lt; 7 Gy</th>
<th>&gt; 7 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>G 2 - 4</td>
<td>7.6%</td>
<td>11.2%</td>
</tr>
<tr>
<td>G 3 - 4</td>
<td>1.3%</td>
<td>3.4%</td>
</tr>
</tbody>
</table>

Orton, 1991
Accelerated Partial Breast Irradiation

• The variety of techniques used can demonstrate the importance of radiobiological principles
  
  – Intraoperative photons
  – Interstitial HDR
  – Single catheter HDR
The importance of radiobiology for dose

- START A trial was used to determine $\alpha/\beta$ ratio of breast tumour
  - Approx 3.4 Gy
- Thus small changes in fraction size can produce large changes in effect of treatment
- Change from multi-catheter interstitial to single channel MammoSite had radiobiologic implications

Courtesy David Wazer
Interstitial Brachytherapy

- Long history of use
- LDR doses converted to HDR using LQ equation
- Dose homogeneity important
- DHI = V100-V150/V100
  - Should be over 75 (over 85 ideal)
- Size of V150 and V200 also important

BEDs and dose gradients.

- Dose/BED is specified at a location (reference point R) which is distant from the sources/dwell positions (S). Doses at points within the prescription isodose will therefore be higher; BEDs higher still.

Between R and S, dose increases according to $1/x^2$. BEDs increase at an even higher rate – very close to the source/dwell position BED increases according to $1/x^4$. Therefore, the effective BED associated with single catheter brachytherapy applications is always higher than that determined at the dose reference point.
Single catheter HDR balloon device

- Inhomogeneous distribution
- EUD concept applies
  - In our series mean EUD 3.5Gy higher than prescribed dose
  - Increased EUD correlated with toxicity
  - EUD decreases with multiple dwell positions and larger balloon sizes
- DHI-only favorable with very large balloons

<table>
<thead>
<tr>
<th>Balloon diameter (cm)</th>
<th>Single dwell position</th>
<th>Multiple dwell positions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BED (Gy&lt;sub&gt;3.6&lt;/sub&gt;)</td>
<td>EQD2 (Gy)</td>
</tr>
<tr>
<td>4.0</td>
<td>77.9</td>
<td>50.1</td>
</tr>
<tr>
<td>4.5</td>
<td>77.7</td>
<td>49.9</td>
</tr>
<tr>
<td>5.0</td>
<td>77.4</td>
<td>49.8</td>
</tr>
<tr>
<td>5.5</td>
<td>77.2</td>
<td>49.6</td>
</tr>
<tr>
<td>6.0</td>
<td>76.9</td>
<td>49.5</td>
</tr>
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</table>
Our series results for RB comparisons

<table>
<thead>
<tr>
<th></th>
<th>BED</th>
<th>EQD2</th>
<th>EUD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Range</td>
<td>Mean</td>
</tr>
<tr>
<td>Tumour (Gy$_{3.6}$)</td>
<td>76.6</td>
<td>65.1-77.8</td>
<td>49.2</td>
</tr>
<tr>
<td>Acute toxicity (Gy$_{10}$)</td>
<td>54.0</td>
<td>46.9-55.0</td>
<td>45.0</td>
</tr>
<tr>
<td>Late toxicity (Gy$_{3}$)</td>
<td>83.6</td>
<td>70.6-84.8</td>
<td>50.2</td>
</tr>
</tbody>
</table>

Intra-Operative Brachytherapy

- LQ equation less accurate predictor at large fraction sizes
- When considering prescribed dose remember Single fraction has similar cell kill to 1/3-1/2 total dose of fractionated RT
- Increased RBE with photons as energy decreases
Relative Effectiveness

Possible Radiobiological Benefits

- Negates risk of accelerated repopulation
- No time for hypoxia to set in
- Geographical accuracy optimal
- Normal tissue protection using lead shields
- Possible favourable alteration of wound environment
Electronic Brachytherapy

- Hotter doses within treatment volume
- Higher V150 and V200s
- Spherical dose, no optimization
- Higher RBE at 1 cm with 50 kV x-rays
- Lower doses beyond PTV volume
- 3.4 Gy x 10 fractions?
- More data needed
Conclusions

• Radiobiology is becoming increasingly important in all aspects of radiotherapy
• More accurate applicators and imaging gives ability for dose escalation—but with due care
• Translational research will be important to identify who may benefit from different techniques
• Long term follow up is essential to determine response and toxicity