Cancer therapy with drugs and/or radiation can damage the structure and functional integrity of the gastrointestinal epithelium, the extent of the damage being dependent upon a number of identifiable variables. Such damage is dose-limiting and limitations on dose may compromise the effectiveness of treatment. All therapeutic schedules represent a pragmatic compromise between damage to tumour and damage to normal tissues. There have been extensive studies on the kinetics of damage and repair of the gastrointestinal epithelium following a variety of insults. Some of these data have already been incorporated into mathematical models.

**ASSESSING DOSE-LIMITING DAMAGE IN THE GUT EPITHELIUM**

Radiotherapy protocols are generally devised according to the tolerance of normal tissues directly exposed to the beam. Recent experimental evidence suggest, however, that cells outside the exposure field are subject to radiation-induced bystander effects, resulting from cell-cell and cell-matrix interactions. The spatial propagation of bystander effects is particularly relevant at low doses, as under these conditions only a small number of cells suffer a “direct hit”. We propose to use mathematical modelling to quantify such DNA-damage-independent effects and estimate the resulting net tolerance of the normal tissue.

**State-of-the-art in modeling radiation effects**

The majority of studies on the mathematical modeling of the effects of radiation on living systems have use a straightforward linear-quadratic (LQ) model of cell killing:

\[ S(D) = \exp(-\alpha D - \beta D^2), \]

with \( S \) the survival function and \( D \) the radiation dose. This represents a pragmatic, but over-simplified, approach with no robust mechanistic foundation. Radiation biologists have failed to exploit the richness of modern mathematical techniques and we believe that we have identified an area, of direct clinical importance, that is ripe for exploitation.

**Questions/suggestions for the Study Group**

- Gradually add new layers of complexity as follows: (1) nonspatial approach, (2) 1D epithelium (i.e. row of cells), and (3) epithelium embedded in 3D tissue.
- Firstly build a biologically-based model describing DNA-damage-mediated radiation effects.
- Then, extend the model to account for DNA-damage independent effects.
- How could the model be used to distinguish between effects on normal and tumour tissues?
- Which parameters have the most dramatic influence on the radiation damage?
- Which parameters play a key role in defining the variation in radiation effects among patients?
**SOME RELEVANT PARAMETER VALUES**

<table>
<thead>
<tr>
<th>Human crypt</th>
<th>Murine crypt</th>
<th>Cell-cycle times</th>
<th>Various</th>
<th>Various</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-60 cells per crypt side</td>
<td>Average 21.9 cells per crypt side</td>
<td>M-phase = 1 hour</td>
<td>Colon epithelium migrates at 5-10µm/h</td>
<td>Spontaneous mutation rate = 10⁻⁹ per base per division</td>
</tr>
<tr>
<td>Total 2000 cells</td>
<td>Total 235-250 cells</td>
<td>G1-phase = 10-14 hours</td>
<td>About 300 cells leave the human crypt per day</td>
<td>Methylation errors = 2×10⁻⁵ per CpG per division</td>
</tr>
<tr>
<td>Basement memb.: 50-100nm thick</td>
<td>Average 18.3 cells per crypt circumference</td>
<td>G2-phase = 2-4 hours</td>
<td>Apoptotic cells are removed in 30-60 min</td>
<td>Human niche succession time = 8.2 years</td>
</tr>
<tr>
<td>Renewal time = 4-6 days</td>
<td>Renewal time = 3-5 days</td>
<td>S-phase = 3-6 hours</td>
<td>Standard radiotherapy regime for large bowel cancer: 45Gy in 25 fractions of 1.8Gy over 5 weeks</td>
<td></td>
</tr>
</tbody>
</table>

**FUTURE APPLICATIONS**

Most schedules currently used in clinical practice have been derived empirically and are employed in a standard fashion, with little account taken of patient-to-patient variation. We suggest that it should be possible, using available biological data in conjunction with mathematical modelling, to devise an approach to treatment scheduling that is more individually based and takes account of patient-to-patient variation in susceptibility to harm. In essence it may be possible to increase the intensity of scheduling for patients who are at lower risk of treatment-related gastrointestinal damage and, conversely, decrease intensity for patients considered to be particularly susceptible to the adverse effects of treatment.

**REFERENCES**