MATHEMATICAL MODELLING OF RADIOTHERAPY STRATEGIES FOR EARLY BREAST CANCER

Heiko Enderling[1], Alexander Anderson[1], Mark Chaplain[1], Alastair J Munro[2] and Jayant S Vaidya[2]

Division of Mathematics[1] and Department of Surgery & Molecular Oncology[2]. University of Dundee

<j.s.vaidya@dundee.ac.uk>

Abstract

Single fraction Targeted Intraoperative radiotherapy (Targit) is a new concept of partial breast irradiation that is being tested in randomised trials. Targit allows accurate dosimetry, avoids delay and has logistic advantages.

We present a mathematical model for growth of a solid tumour in breast, its surgical excision and adjuvant radiotherapy. We use the linear quadratic model to compute the survival probabilities for both tumour cells and breast tissue and simulate the effects of external beam radiotherapy and Targit.

Local recurrence could arise from stray tumour cells or from morphologically normal cells in the tumour bed that harbour predisposing genetic changes, such as loss of heterozygosity on tumour suppressor genes (LOH).

Our mathematical model predicts that Targit would eliminate all these sources of recurrence, whereas the fractionated external beam radiotherapy would eliminate stray tumour cells, but allows the cells with LOH to accumulate radiation induced DNA damage.

Our work is an initial attempt to model a biologically complex phenomenon that has until now received little attention in the literature. We hope to extend our model to 3-dimensions and to the cellular level in tandem with molecular experiments to study normal tissue effects of radiotherapy that are ongoing at our centre.

Nature of the collaboration

H Enderling has an applied computing background with expertise in numerical simulations and high-dimensional scientific visualization. ARA Anderson and MAJ Chaplain are mathematical biologists with exceptional knowledge in modelling tumour growth and invasion and angiogenesis.

JS Vaidya is a senior lecturer and consultant surgeon with keen interest in radiobiology of intra-operative radiotherapy, origin of local recurrence and mathematical modelling. He initiated the Targit trial[1] and an active member of the steering committee. AJ Munro is a radiation oncologist and consultant radiotherapist with current research interests in intra-operative radiotherapy and predictive assays for normal tissue damage in radiotherapy. Deep theoretical discussions within our group are remarkably easy.

With this collaboration we unite outstanding interdisciplinary knowledge that is necessary to model biological, medical, and radiotherapeutic problems on a theoretical level to predict and compare different radiotherapy treatment strategies for early breast cancer patients.

Background

External beam radiotherapy

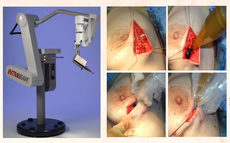
Patients undergoing breast conserving surgery routinely receive external beam radiotherapy (EBRT). This adjuvant radiotherapy is supposed to eliminate cancer cells that were 'left behind' and therefore prevent local recurrence. EBRT is given as fractionated treatment of 2 Gy each day over 4-6 weeks. Fractionation allows normal cells to recover from the effects of the low dose of each delivery of radiotherapy. Without EBRT, 39% patients[2] will get local recurrence.

Targit- the technique -Intrabeam™

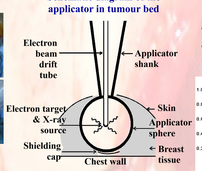
A miniature electron generator and accelerator that delivers *soft x-rays (50kV)* from within the breast.

The pliable breast tissue wraps around the applicator achieving true conformal brachytherapy.

The procedure is performed in a standard operation theatre in 25-30 min while the patient is anaesthetized.



Schematic diagram of the applicator in tumour bed



- The Targit trial is based on the finding that 91% of local recurrence after breast conserving therapy occurs at the site of the primary tumour. It being compared with standard 5-6 week course of EBRT.
- Up to 50% of local recurrence may be attributable to missing of the target tissues by EBRT. Accurate targeting of radiotherapy with Targit may prevent this.
- Many women are forced to choose mastectomy, just because they live far from a radiotherapy centre- so a single session of radiotherapy may allow them to benefit from breast conserving surgery.
- Preliminary cosmetic results have been excellent.
- This is new technology is cheaper and may actually save money.

Hypothesis

Traditionally local recurrence is presumed to originate from 'stray' tumour cells. However, with modern surgery and histopathology, clear margins are very carefully ascertained and further surgery is undertaken if any margin is found to be involved with microscopic tumour. So patients undergoing surgery for breast cancer – either conserving the breast or mastectomy, are very unlikely to have any part of the original tumour to be left behind in the breast. If the possibility of leaving residual disease is so small then where does the local recurrence come from and what does the adjuvant radiotherapy actually treat?

It appears that post-operative radiotherapy mainly targets the 'normal tissues' in the tumour bed.

We know that cells in the tumour bed are morphologically normal but may harbour loss of heterozygosity in tumour suppressor genes (LOH)[3].

We hypothesise that these cells could be the origin of tumour recurrence. We set out to create a mathematical model of the effect of different radiotherapy strategies on tumour bed that includes some traditional 'stray' tumour cells as well as normal looking but genetically mutated cells.

Why a model?

Although there are some mathematical models for fractionated radiotherapy, there is no reliable model to compare shorter durations or single fraction radiotherapy. Therefore, designing of new treatment strategies has to rely only on empirical 'wisdom and logic'.

Mathematical models of radiotherapy have the potential to identify dangerous treatment schedules, optimize the treatment outcome, or design better clinical trials. They could also be used in conjunction with new molecular biological knowledge as we have demonstrated in this paper.

Mathematical Model[4]

Three different phases

- solid tumour invading the host breast tissue
- surgery and radiation therapy
- development (or not) of local recurrence

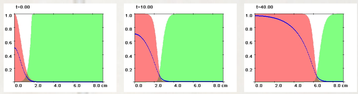
Phase I: Simulation of solid tumour growth and invasion.

The invasion model considers tumour cells *[denoted as n]*, extracellular matrix (ECM) *[f]* and matrix-degrading enzymes (MDE) *[m]*:

Tumour cell density
$$\frac{\partial n}{\partial t} = \overbrace{\lambda n(1-f-n)}^{\text{proliferation}} + \overbrace{d_n \nabla^2 n}^{\text{radom motility}} - \overbrace{\gamma \nabla \cdot (n \nabla f)}^{\text{haptotaxis}}$$

ECM density
$$\frac{\partial f}{\partial t} = \overbrace{-\eta m f}^{\text{degradation}}$$

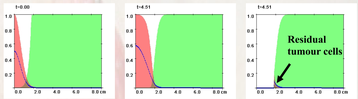
MDE concentration
$$\frac{\partial m}{\partial t} = \overbrace{d_m \nabla^2 m}^{\text{diffusion}} + \overbrace{\alpha n(1-m)}^{\text{production}} - \overbrace{\beta m}^{\text{decay}}$$



Simulation of solid tumour growth and invasion in Phase I of our model framework. Tumour cells (red) proliferate and invade the surrounding tissue (green). The matrix degrading enzymes (solid blue line) degrade the tissue to make space for the tumour to grow into. t=1 means 1 year. Brown represents the tumour margin.

Phase II: Surgery

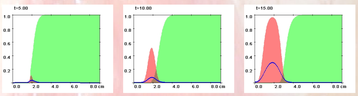
Let us assume the tumour develops as described and reaches a size of 2cm. At this stage we model breast conserving surgery.



Simulation of surgery for early breast cancer. When the dense tumour (red) reaches 2 cm as in the middle figure, surgery is simulated and all cells and enzymes in the area of high tumour tissue density are removed– as in the last figure. The 'stray' tumour cells in the tissue after surgery are represented by the small brown triangle at the bottom left of the green area near the x-axis.

Phase III: Re-growth in the absence of adjuvant radiotherapy

Without radiotherapy the stray tumour cells in the adjacent tissue proliferate causing local recurrence.



Simulation of the recurrence of a breast tumour (red) when there are a few tumour cells left behind in the tissue (green) during surgery as shown in the figure above. The matrix degrading enzyme density is plotted as the blue line.

Modelling Radiotherapy

- We use the established linear-quadratic (LQ) model to calculate tumour and tissue surviving fractions.
- Tumour and tissue dynamics between fractions in conventional treatment are simulated by the mathematical model as shown above.
- We consider every fraction independently.

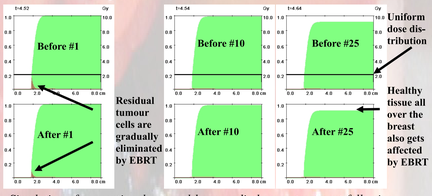
The biologically effective dose (BED) is obtained from the LQ-relations:

$$BED = n\,x\,d\,(\alpha+\beta d)$$

where d is the delivered dose, n is the total number of fractions (1 in our case), α is the coefficient of single-hit double strand breaks and β is the coefficient of the combination of two sub-lethal double-strand breaks.

Conventional treatment: External Beam Radiotherapy:

- 25 fractions each of 2Gy delivered over 5 weeks
- time between fractions gives healthy tissue time to recover from damage

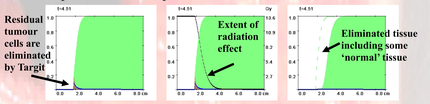


Simulation of conventional external beam radiotherapy treatment following breast conserving surgery (top left). Fractions with doses of 2 Gy each (solid black line in the top pictures) are delivered to the whole domain eradicating all tumour cells (brown) but also harming the healthy (green) breast tissue (bottom row).

From left to right: fractions 1, 10 and 25. The number of fractions needed to eliminate the residual tumour cells depends on the original tumour burden.

Targeted intra-operative Radiotherapy:

- A single large fraction delivered with soft X-Rays over 20 minutes.
- The rapid dose fall off spares distant tissues.



Centre: Initial distribution and coverage of radiation (black line). The rapid attenuation of the dose protects distant tissues (green). Right: the domain after irradiation. Tumour cells are completely killed. The damage of breast tissue due to irradiation is very localised. The dashed line represents the pre-treatment healthy tissue margin.

Justification of Financial Request

Support is requested for post-doctoral post of HE who has been involved with this work and has the necessary knowledge and skills to take forward the project, and for upgrade of the existing computer system so that the high-computational demand for 3-dimensional modelling is made available. A third of his salary is already in place.

Post-doc Mathematical biologist (2/3 WTE)	18118
Conference registration / travel budget	800
Technical equipment upgrade	500
TOTAL	19418

Mutations in adjacent tissue

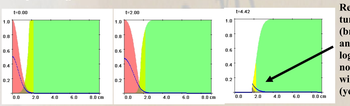
- Loss of heterozygosity (LOH) in tumour suppressor genes (TSGs) has been identified recently as strong indicator for local recurrence
- Breast tissue is clonal and develops during puberty
- Mutations accumulated before puberty can spread throughout the segment of the gland during clonal development at puberty and then during pregnancy
- If a mutation (for example LOH) occurs on tumour suppressor gene all 'daughter' cells more susceptible for further mutative hits

Only a few stem cells for the mature breast via cloning. If for example the yellow stem cell features LOH in TSGs, all 'daughter' cells have the same genetic instability that makes these cells more susceptible for further mutative hits which can lead to a primary tumour formation. As seen on the right picture, cells in the tissue adjacent to the tumour are clones from the same stem cell and thus harbour the same crucial mutations.

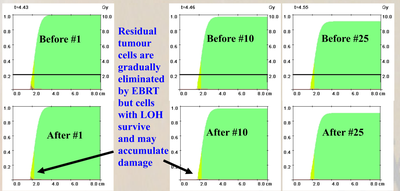
Irradiation of cells harbouring LOH in TSGs :

Crucial cell-cycle check points are disabled in cells with LOH in TSGs. Therefore, these cells can accumulate sub-lethal damage induced by low radiation dose of each fraction of EBRT.

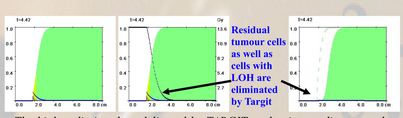
A severe double-strand break induced by a high dose could irrevocably damage these cells.



Initial tumour growth (1st and 2nd figures) and surgery with the yellow region representing cells in the tumour bed that have LOH in tumour suppressor genes and are likely to be share clonality with the original tumour.



From left to right: Results of EBRT after fractions 1, 10 and 25. Cells with LOH on TSG not only survive the irradiation, but could also accumulate low-dose radiation induced mutations.



The high radiation dose delivered by TARGIT to the tissue adjacent to the primary tumour causes enough damage to eradicate both the residual tumour cells as well as genetically unstable cells in the tumour bed.

Conclusion from our initial model

- Our simulations have shown that on a macroscopic level that Targit is at least as successful as EBRT in eradicating stray tumour cells in the tumour bed.
- In addition, single fraction irradiation with Targit also eradicates cells with genetic mutations like loss of heterozygosity in tumour suppressor genes and thus eliminates another potential source of recurrence.
- Our model predicts that Targit could be superior to conventional radiotherapy especially for preventing within-scar recurrence.
- Further work in this area is necessary to simulate individual cell behaviour.
- In addition, modelling in 3-dimensions with breast specific tissue parameters could enable a better demonstration the geometrical distribution of effects of radiotherapy.

Related papers from the group

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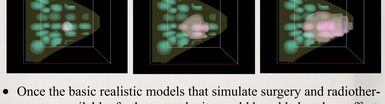
2. Fisher B, Anderson S, Bryant J et al, 2002 Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer N Engl J Med. 347(16):1233-41.
3. Li, Z., Moore, D.H., Meng, Z.H., Ljung, B.M., Gray, J.W., Dairkee, S.H., 2002. Increased risk of local recurrence is associated with allelic loss in normal lobules of breast cancer patients. Cancer Research 62, 1000–1003.
4. Enderling, H., Anderson, A.R.A., Chaplain, M.A.J., Munro, A.J., Vaidya, J.S., 2005. Mathematical modelling of radiotherapy strategies for early breast cancer. J. Theor. Biol, Accepted pending revision.

Follow up Work



- Once the basic realistic models that simulate surgery and radiotherapy are available, further complexity could be added such as effect of neoadjuvant hormone or chemotherapy, differing tumour parameters such as grade and infiltrative edge; different tissue characteristics such as mammographic breast density, etc.
- This model could improve communication of new ideas between mathematicians, surgeons, oncologists and medical physicists devising new radiotherapy strategies, and help patients better understand their treatments.