UNIVERSITY OF CAMBRIDGE

UNIVERSITY OF SURREY

TREATMENT PLANNING

Modelling chemo-hadron therapy

Lara Barazzuol | Valencia | 19 June 2009

Contents:

UNIVERSITY OF SURREY

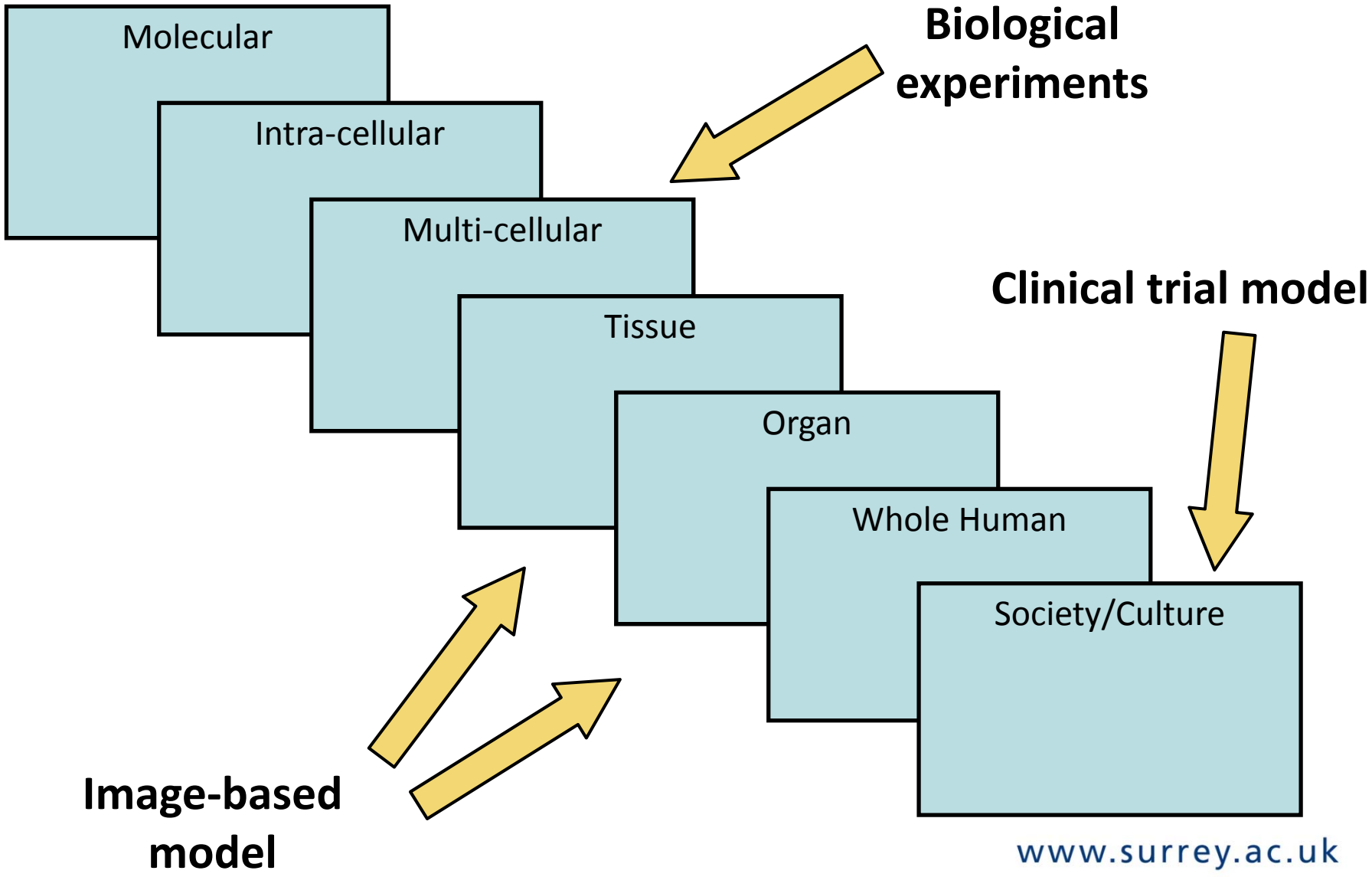
- Background - PARTNER project
- Glioblastoma & treatment
  - Research questions
- Clinical Trial model: outline
  - Temozolomide: Scenarios 1 and 2
  - Clinical trial model conclusions
- Further work
  - Effects of concurrent chemo-hadron therapy
  - TMZ radiosensitization in T98G cells
  - Image-based model

Background:

UNIVERSITY OF SURREY

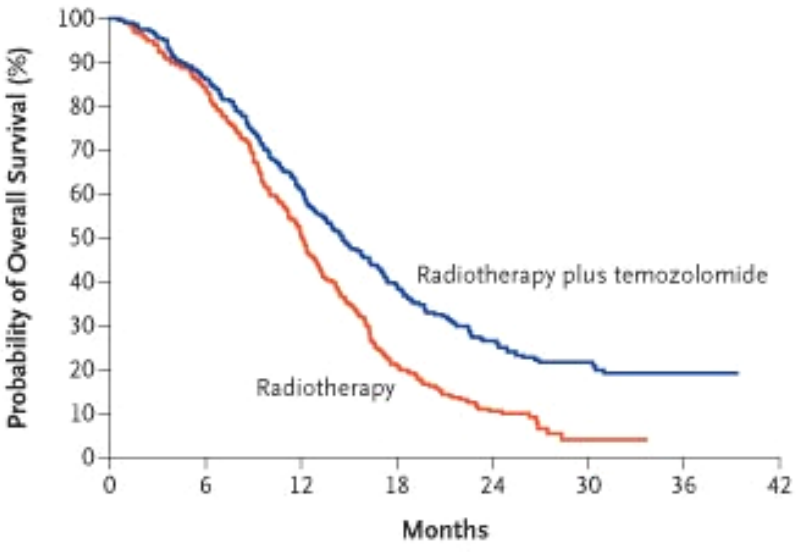
- BSc - Biomedical engineering at the University of Padova, Italy
- MSc - Bioengineering at the University of Padova, Italy
- MSc project at the University of Surrey, UK - modelling brain tumour response to radiotherapy and chemotherapy considering radiobiological aspects
- PARTNER project - treatment planning:
  - modelling concurrent chemo-radiotherapy and chemo-hadron therapy
  - measuring effects of concurrent chemotherapy on cell survival for a variety of ions

Mathematical models & biology:



Glioblastoma & treatment:

- Most frequent and malignant adult primary brain tumour
- For many years, the conventional treatment has been maximal surgical resection followed by radiotherapy (RT)
- In 2005 a phase III trial (EORTC-NCIC) has confirmed the benefit of temozolomide (TMZ) chemotherapy: increase of 16.1 % in 2 year survival, for patients receiving RT with TMZ compared with RT alone



No. at Risk							
Radiotherapy	286	240	144	59	23	2	0
Radiotherapy plus temozolomide	287	246	174	109	57	27	4

(Stupp et al. 2005)

RT alone: 60 Gy

RT + TMZ: 60 Gy +
Concurrent TMZ+
6 cycles of TMZ alone

Research questions:

- What is the optimum combination and scheduling of RT and TMZ?
- Does the major benefit of TMZ come from the concurrent phase or the six cycles of adjuvant TMZ?
- Does TMZ sensitise glioblastoma to the effects of radiotherapy?
- Is the 6 months of adjuvant TMZ working independently to kill cancer cells?
- Which are TMZ effects with protons or heavier ions?

Mathematical models and radiobiological experiments can help us to elucidate TMZ role

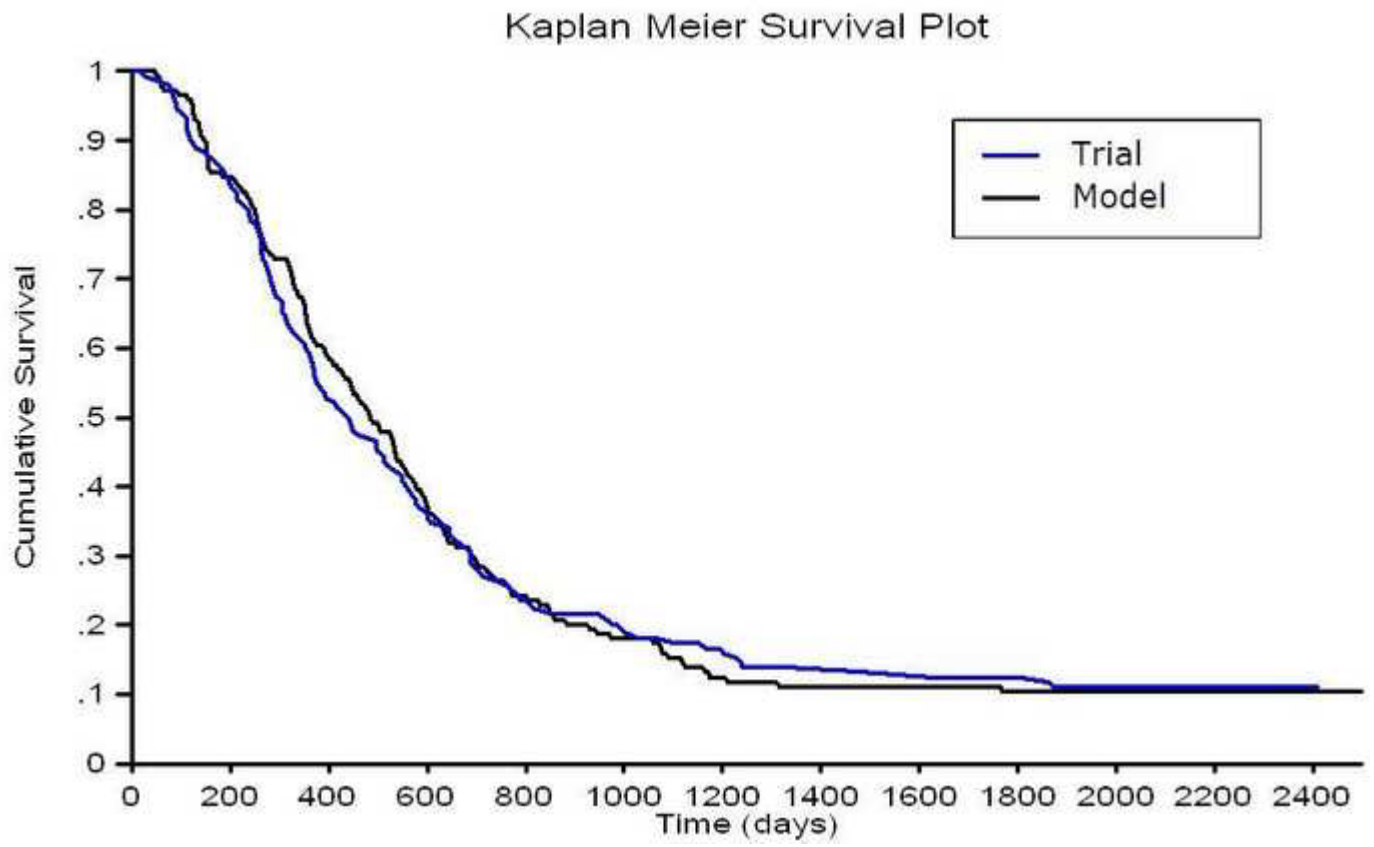
Clinical trial model: outline

1. Individual patient and treatment model:
   - first order interaction between cancer and normal cells
   - tumour response to radiotherapy and chemotherapy
   - response to delay before treatment
2. Simulation of *in silico* trial:
   - Monte Carlo simulation to generate a population of patients
3. Fitting to real clinical survival data:
   e.g. EORTC-NCIC trial, two arms:
   - RT alone
   - RT + concomitant and adjuvant TMZ

Temozolomide - Scenario 1:

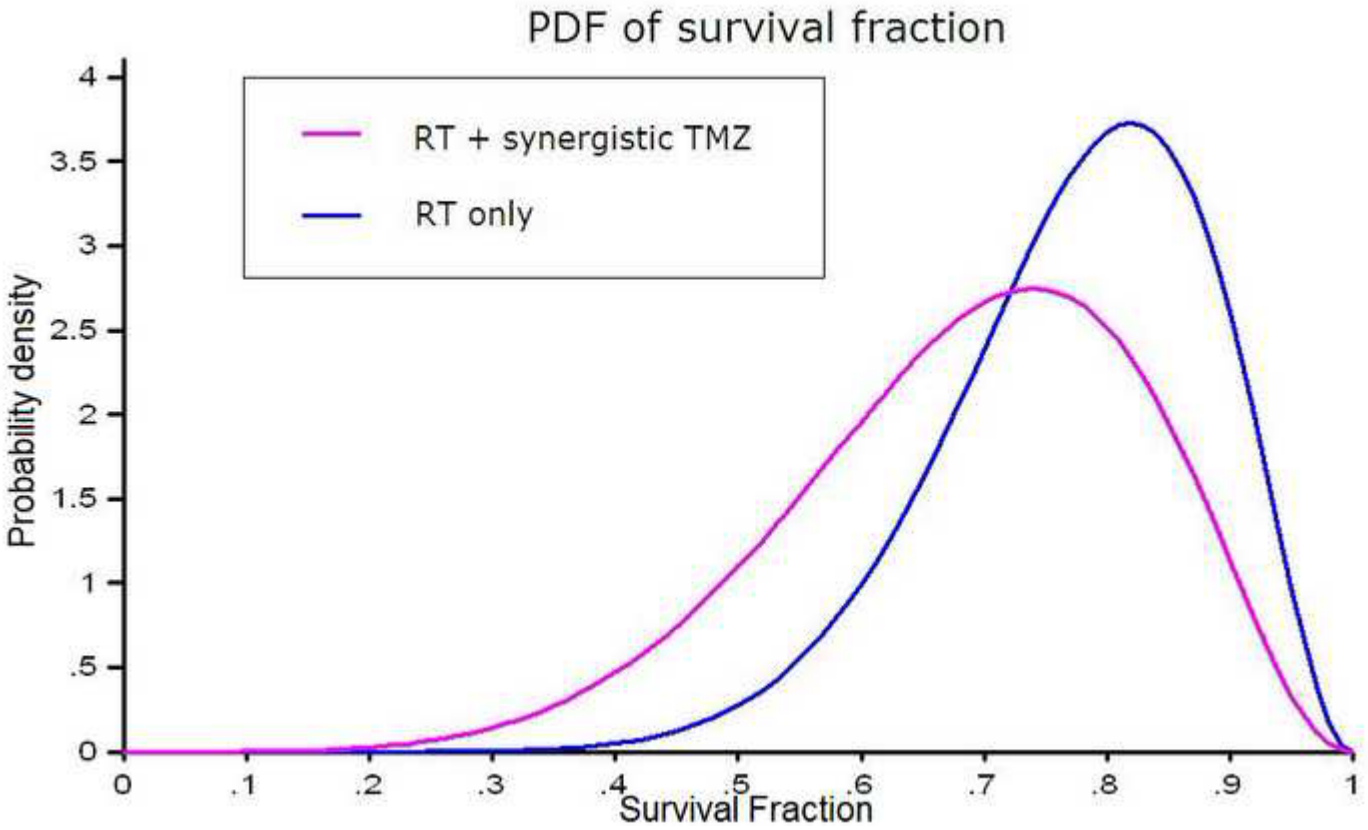
TMZ mediated-radiosensitization:

- change in the α/β ratio
- concomitant phase



Temozolomide - Scenario 1:

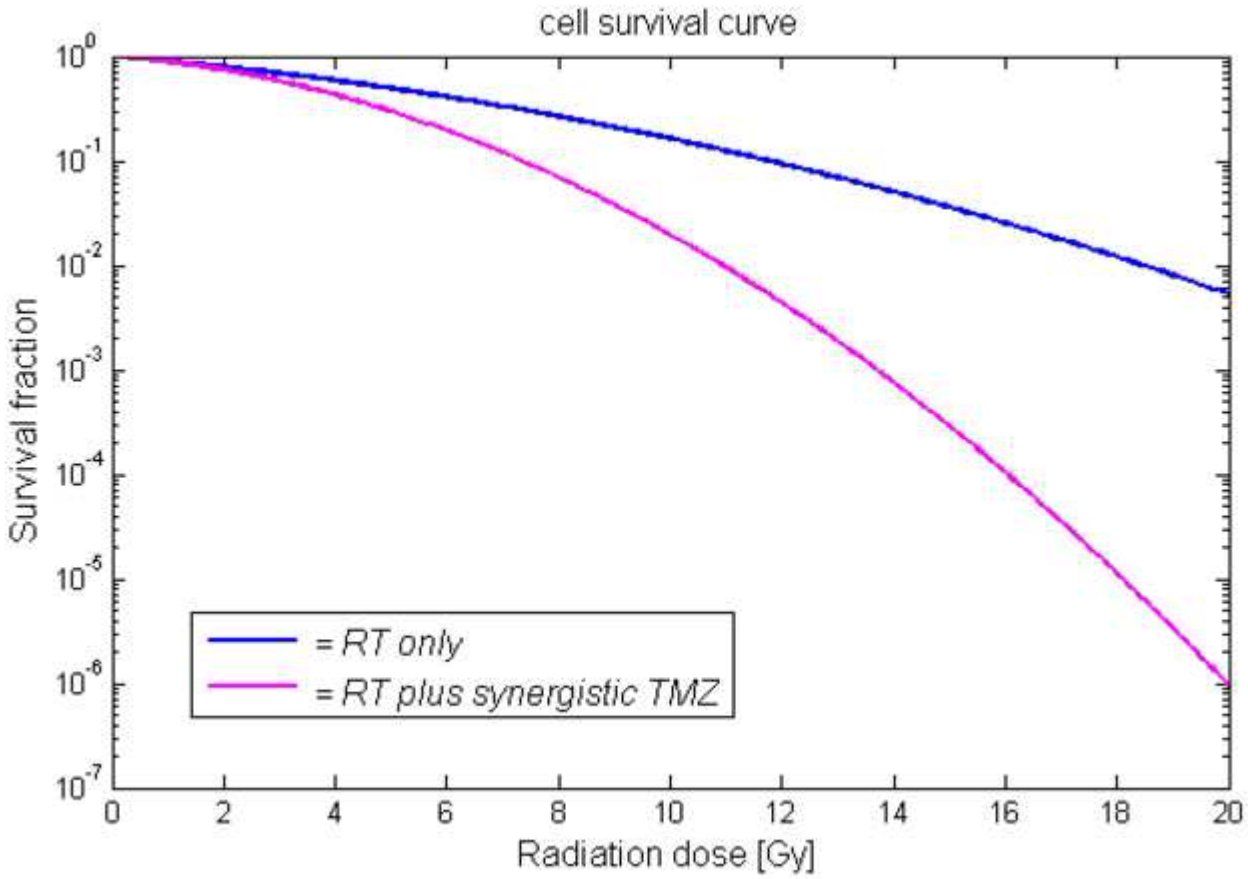
Comparison of the probability distributions of survival fraction, after a single 2 Gy fraction of RT



Temozolomide - Scenario 1:

Synergy between RT and TMZ:

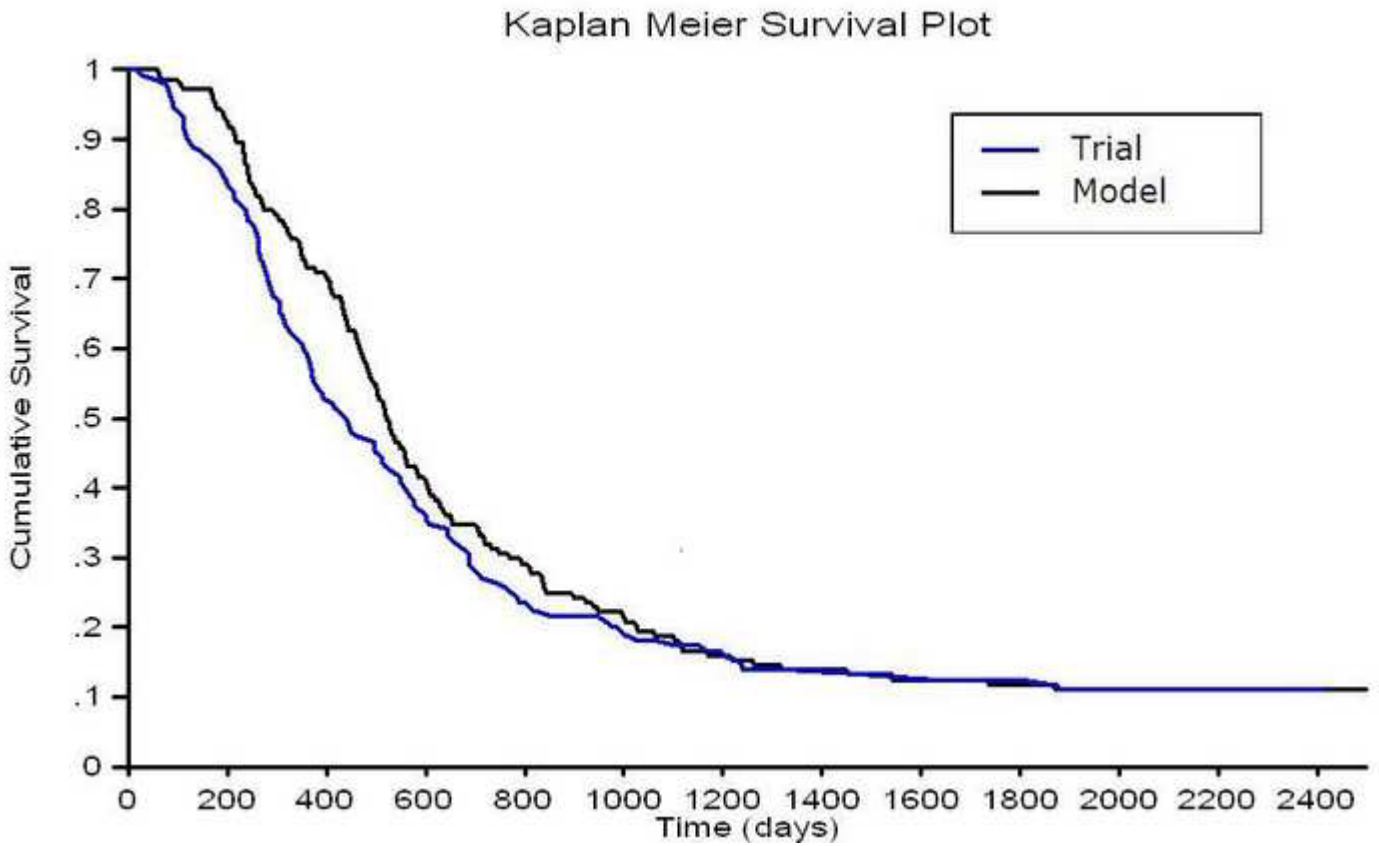
- α/β decreases from 12.5 Gy to 3.1 Gy



Temozolomide - Scenario 2:

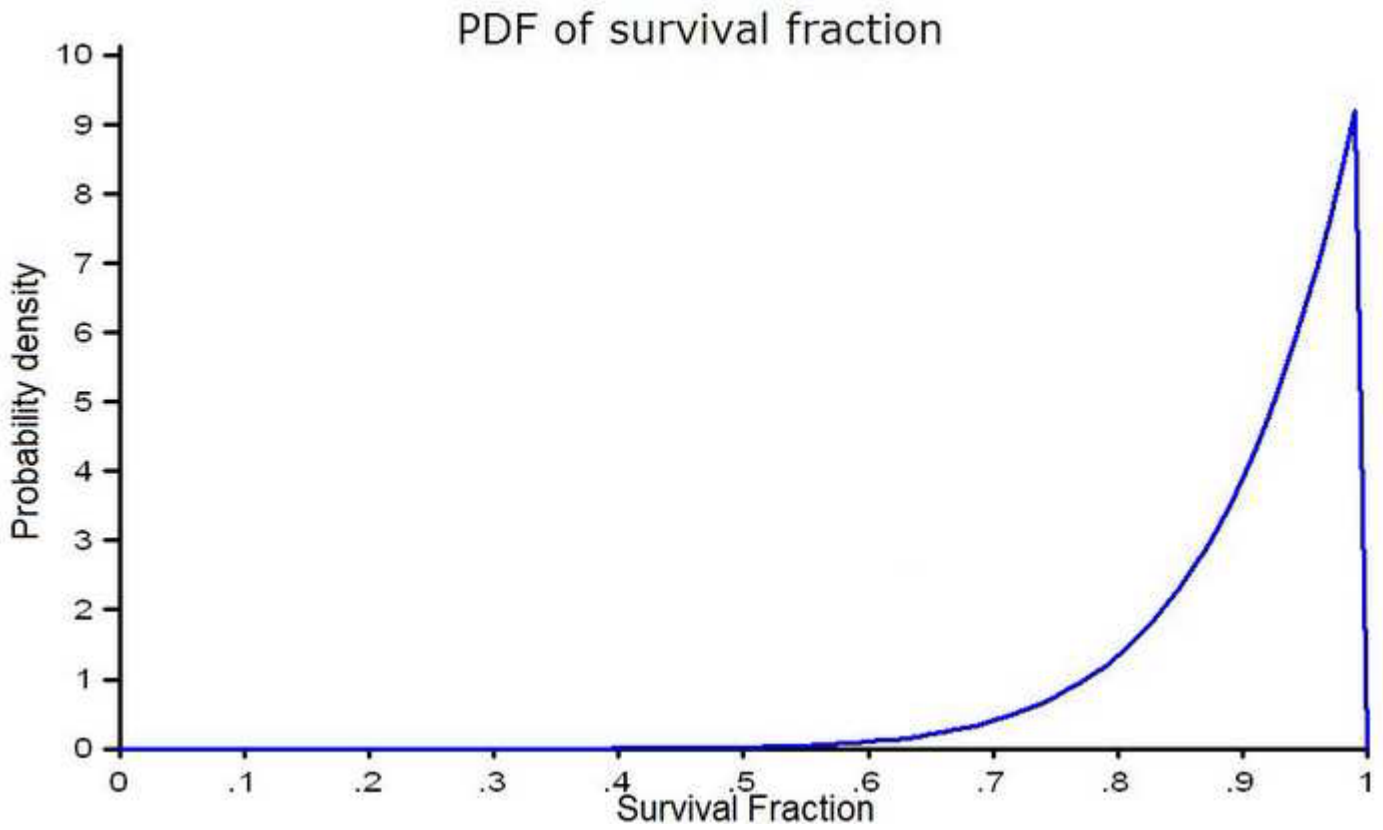
TMZ independent cytotoxicity:

- simple PK/PD model
- adjuvant phase



Temozolomide - Scenario 2:

Probability distribution of the chemo-sensitivity resulting from fitting to the RT+TMZ data



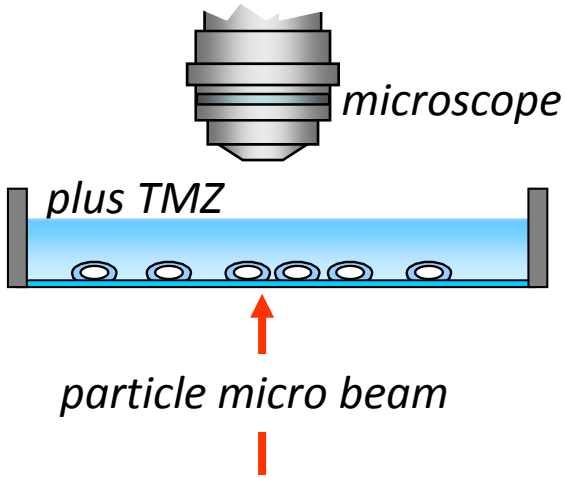
Clinical trial model-conclusions:

1. The EORTC-NCIC trial analysed with our model suggests that TMZ is mainly a radiosensitiser
   - hence the activity of TMZ as single agent seems to have a more marginal benefit
2. Major therapeutic efficacy of the concomitant phase
   - little value in giving neo-adjuvant or adjuvant TMZ
3. TMZ addition appears to change the radiobiological parameters
4. Not yet clear how much better fully co-optimised RT and TMZ could be...

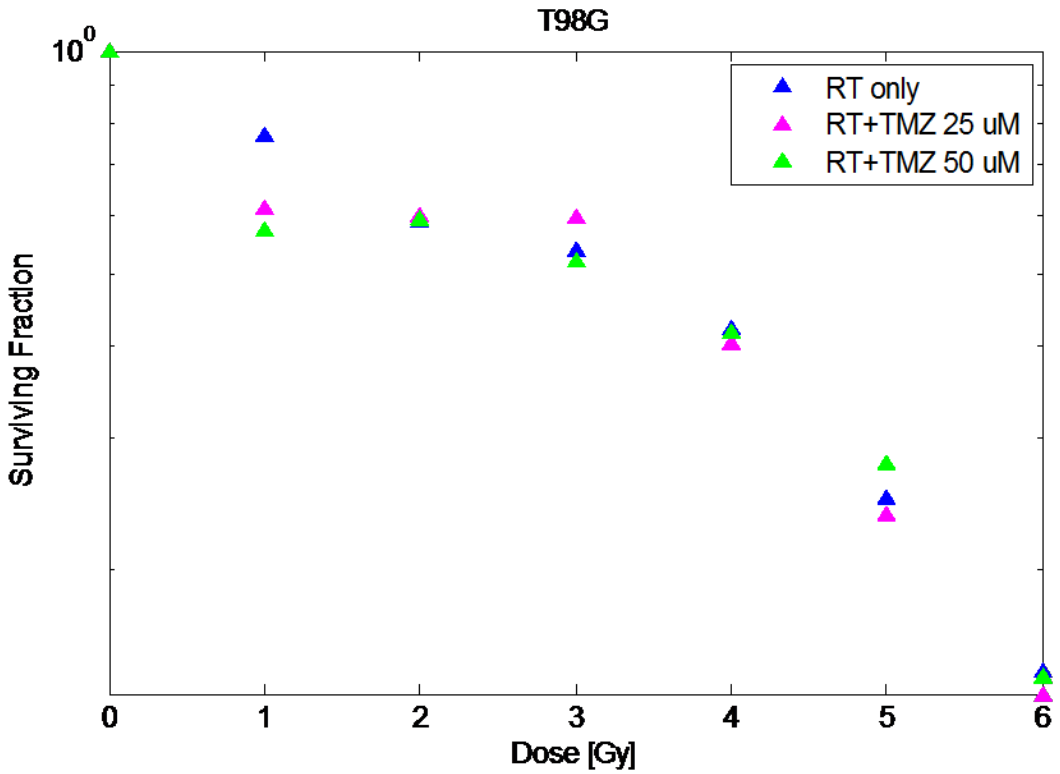
Further work:

- We can use the model to evaluate and design new clinical trials: e.g. - outcome of the dose-dense TMZ trial;
  - possible palliative RT+TMZ trial;
  - RT dose escalation given the apparent change in the α/β ratio (e.g. 74 Gy in 6 weeks + TMZ);
  - modelling interruptions in treatment.

- We can look at TMZ synergy with protons or heavier ions vs. photons using the vertical ion beam line

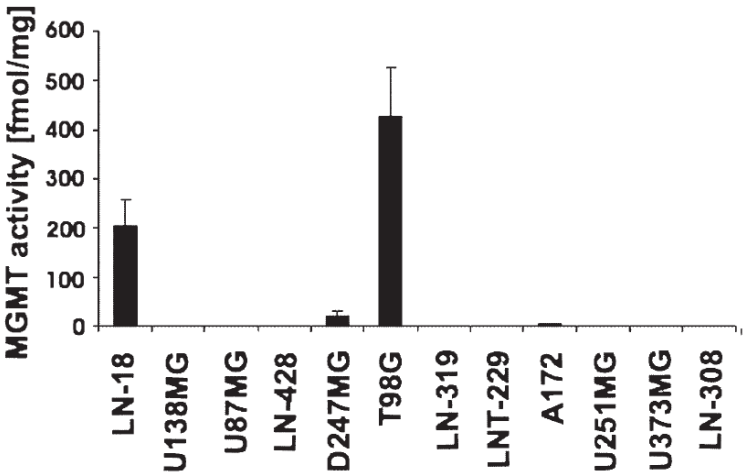


TMZ-radiosensitisation in T98G cells:



- T98G cells: human glioblastoma
- RT: 1-6 Gy, Pantak kV unit
- TMZ: 25-50 µM

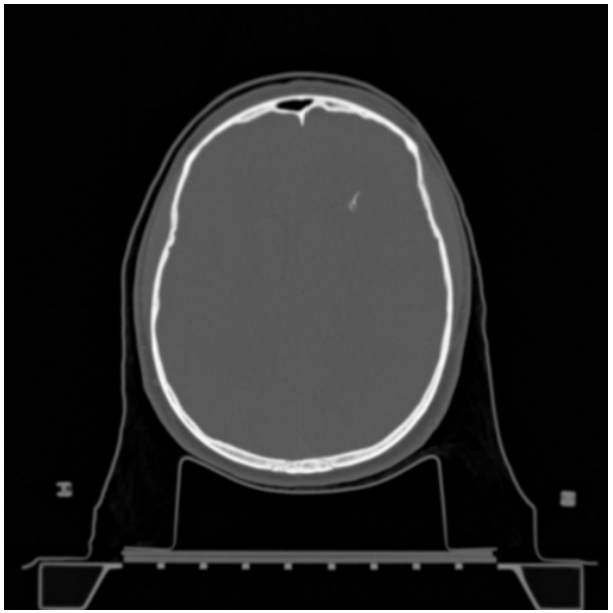
- MGMT status: prognostic factor
  - unmethylated MGMT promoter: little or no benefit from TMZ
- T98G cells exhibit the highest MGMT activity

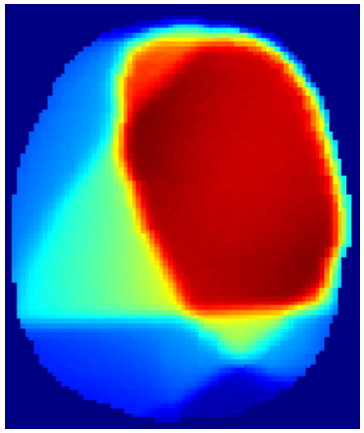


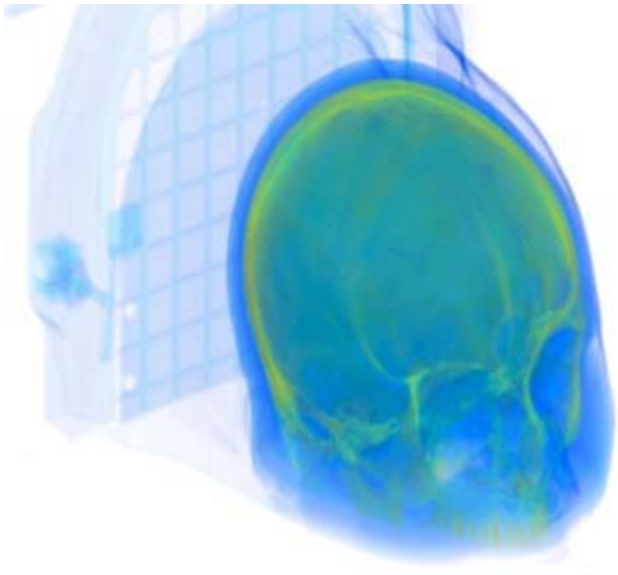
(Hermissson et al. 2006)

Image-based model:

A model based on IMRT-IMPT images to estimate tumour control probability (TCP) and normal tissue complication probability (NTCP) using radiobiological information: SF values (e.g. with or without TMZ, in hypoxic conditions, with heavier ions...)







Acknowledgements

- The Addenbrooke's Hospital
- The Department of Oncology, University of Cambridge
- The Royal Surrey County Hospital
- Marie Curie Research Training Network 'PARTNER'
- The Gray Cancer Institute
- Surrey Ion Beam Centre
- The Wolfson Foundation
- The Health Foundation