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Doctoral Thesis

Development of an Integrated Stochastic Model for the Evaluation of the Impact of Microscopic Extension on Tumour Clonogen Survival in Heterogeneous Hypoxic Glioblastoma Multiforme

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Declaration of Authorship

I, Leyla Moghaddasi, certify that this thesis titled, 'Development of an Integrated Stochastic Model for the Evaluation of the Impact of Microscopic Extension on Tumour Clonogen Survival in Heterogeneous Hypoxic Glioblastoma Multiforme ' and the work presented in it are my own. I confirm that:

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I believe in intuition and inspiration. Imagination is more important than knowledge. For knowledge is limited, whereas imagination embraces the entire world, stimulating progress, giving birth to evolution. It is, strictly speaking, a real factor in scientific research.

Albert Einstein

Abstract

Determination of an optimal Clinical Target Volume (CTV) margin is generally challenging since the exact extent of microscopic disease to be encompassed by the CTV cannot be fully visualized using current imaging techniques and therefore remains uncertain.

The aim of this work was to establish a treatment-modelling framework for evaluation of current CTV practices in terms of tumour clonogen survival fraction following treatment. An integrated radiobiological model has been developed for this purpose, using the Monte Carlo (MC) toolkit Geant4. In order to determine the tumour site with high discrepancy/uncertainty in terms of the CTV margin definition, a comprehensive literature review was conducted. As a result, Glioblastoma Multiforme (GBM) was identified to be the subject of this research work.

Model Development

The architecture of the MC model consists of three main components: 1) simulation of a GBM tumour with diffusions of tumour cells beyond the limit of the CTV, called Microscopic Extension Probability (MEP) model; 2) irradiation of the GBM model; and 3) cell survival calculation.

GBM treatment modelling using 6 MV conventional X-ray therapy

A model of GBM and its microscopic extension was developed using MATLAB® (MathWork® Natick, MA). The input parameters required for the simulation were obtained from published clinical literature data. The MC toolkit Geant4 was used for the second component of the model. The input code enabled simulation of geometry (i.e. the GBM model), the radiation beam , and detailed transport of each particle tracked throughout the geometry until coming to rest. As a result absorbed dose was calculated in individual cells. In the third component of the model, predicting survival probability for each individual tumour cell within the *in silico* model, was achieved using a combination of Matlab codes developed in this work and Geant4 outputs imported into Matlab. The Linear Quadratic (LQ) model was used to calculate cell survival probabilities.

Homogeneous and normoxic GBM

The first study considered a simplified model of GBM consisting of a population of cells with homogeneous radiosensitivities represented in terms of α and β parameters of the LQ model. At this stage of the study, hypoxic cells were not considered. A Geant4 cellular model was developed to calculate the absorbed dose in individual cells represented by cubic voxels of 20 μm sides. The system was irradiated with opposing 6MV X-ray beams. The beams encompassed planning target volumes corresponding to 2.0 and 2.5 cm CTV margins. As a result, Survival Fraction (SFs) following x-ray EBRT were calculated for various simulation set-ups including different cellular p53 gene status, CTV margin extensions and ME propagations in regions of interest.

Heterogeneous and hypoxic GBM

The next stage of the project focused on expanding the GBM model to incorporate other radiobiological parameters affecting cellular radiosensitivities. Oxygenation and heterogeneous radiosensitivity profiles were incorporated into the GBM model. The genetic heterogeneity was modelled using a range of α/β values associated with different GBM cell lines, obtained from published clinical data. Cellular oxygen pressure taken from a sample weighted to literature-based profiles was randomly distributed. Three types of GBM models were analysed: homogeneous-normoxic, heterogeneous-normoxic, and heterogeneous-hypoxic. The SF in different regions of the tumour model and the effect of the CTV margin extension from 2.0 – 2.5 cm on SFs were investigated for three MEP models.

The results of this study for a virtual GBM model suggested that radiobiological damage caused by x-ray beams may not be sufficient to kill or sterilize GBM cell populations, and the tumour is most likely to relapse in the treatment volume. Therefore, the ultimate aim of the x-ray therapy of these tumours may be extension of time to recurrence rather than cure. This conclusion led the direction of the study to another modality which could potentially offer more promising treatment outcome for GBM.

GBM treatment modelling using Boron Neutron Capture Therapy

Recent technological advances have enabled other modalities to be developed, including charged particle radiation and targeted therapies, to be developed. Boron Neutron Capture Therapy (BNCT) is a biochemically-targeted type of radiotherapy where thermal neutrons are captured by ^{10}B, resulting in the emission of high Linear Energy Transfer (LET) α-particles and re-coiling ^{7}Li nucleus. This is a binary modality in which a suitable ^{10}B agent is taken up preferentially by malignant cells. The clustered damage produced by high LET radiation could selectively destroy cancer cells dispersed in normal tissue, with minimal normal tissue toxicity. This makes BNCT an appropriate modality for infiltrative GBM.

A realistic neutron beam model was developed in Geant4 and verified against published data. The system was defined as a cubic phantom divided to 20 μm side voxels (the average size of glioma cells) and irradiated with an epithermal neutron beam. Typical ^{10}B concentrations in GBM and normal brain cells were obtained from literature. Each cell was then assigned a ^{10}B concentration depending on its MEP status. Nested parameterisation method was used, to assign each cell with its corresponding material, which was built in Geant4 using brain composition with added boron atoms. Results from the cell-based dosimetry model and the MEP models were combined to evaluate SFs for CTV margins of 2.0 & 2.5 cm, and different infiltration distributions in regions of interest.

Conclusion

A novel Monte Carlo-based approach has been employed by this project aiming to address a clinically important question. The integrated GBM radiobiological model is a tool to quantitatively evaluate the impact of different CTV margins for GBM on cancer cell survival. It is believed that the information acquired during this research will be useful for clinicians to optimize treatment prescription for glioblastoma multiforme patients using x-ray therapy and boron neutron capture therapy.

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Abbreviations

BNCT	**B**oron **N**eutron **C**apture **T**herapy
CPU	**C**entral **P**rocessing **U**nit
CT	**C**omputer **T**omography
CTV	**C**lincal **T**arget **V**olume
DNA	**D**eoxyribo**n**ucleic **A**cid
DSB	**D**ouble **S**trand **B**reak
EBRT	**E**xternal **B**eam **R**adio**t**herapy
GEANT	**Ge**ometry **an**d **T**racking
GPU	**G**raphics **P**rocessing **U**nit
GTV	**G**ross **T**umour **V**olume
IGRT	**I**ntensity **G**ated **R**adio**t**herapy
IMAT	**I**ntensity **M**odulated **A**rc **t**herapy
IMRT	**I**ntensity **M**odulated **R**adio**t**herapy
LET	**L**inear **E**nergy **T**ransfer
LPL	**L**ethal **P**otentially **L**ethal
LQ	**L**inear **Q**uadratic
MC	**M**onte **C**arlo
MRI	**M**angetic **R**essonance **I**maging
OER	**O**xygen **E**nhancement **R**atio
PC	**P**ersonal **C**omputer
PDF	**P**robability **D**ensity **F**unctions
PET	**P**ositron **E**mission **T**omography
PTV	**P**lanning **T**arget **V**olume
RAM	**R**andom **A**ccess **M**emory

RBE **R**elative **B**iological **E**ffectiveness

Physical Constants

Speed of Light	c	=	$2.997\ 924\ 58 \times 10^{8}$ ms^{-1}
Gravitational Constant	G	=	$6.673\ 84 \times 10^{-11}$ m^{3} kg^{-1} s^{-2}
Plank's Constant	h	=	$6.626\ 069\ 57 \times 10^{-34}$ m^{2} kg s^{-1}
Fine Structure Constant	α	=	$7.297\ 352 \times 10^{-3}$
Electron Rest Mass Energy	m_e	=	510.99 keV
Proton Rest Mass Energy	m_p	=	938.27 MeV
Neutron Rest Mass Energy	m_n	=	939.56 MeV
Alpha Particle Rest Mass Energy	m_α	=	3727.37 MeV
Charge of an Electron	e	=	1.6021×10^{-19} C
Classical Electron Radius	r_e	=	$2.817\ 940 \times 10^{-15}$ m
Bohr Radius	a_0	=	0.529177×10^{-10} m
Compton Wavelength	λ_C	=	2.426×10^{-12} m
Stefan-Boltzmann Constant	σ	=	$5.670\ 373 \times 10^{-8}$ W m^{-2} K^{-4}
Boltzmann Constant	k	=	$1.380\ 658 \times 10^{-23}$ J K^{-1}
Rydberg Constant	$\mathfrak{R}$	=	$10\ 973\ 731.568 \times 10^{-1}$ m^{-1}
Avogadro's constant	N_A	=	6.0221×10^{23} mol^{-1}
Permittivity of Free Space	ϵ_0	=	8.8541×10^{-12} F m^{-1}
Permeability of Free Space	μ_0	=	$12.566\ 370 \times 10^{-7}$ N A^{-2}
Gas Constant	R	=	8.3144 J K^{-1} mol^{-1}

Symbols

D	Absorbed radiation dose	Gy
P	Power	Watts
SF	Survival fraction	(dimensionless)
E	Particle energy	MeV
σ	Interaction cross section	cm^{-1}
Z	Atomic number	(dimensionless)
T	Kinetic energy	MeV
B	Binding energy	eV

Dedicated to my beloved late aunt, Fatemeh Borghei, whose accomplished life was cut short too soon by lung cancer. She was a brilliant astrophysicist and her beautiful mind is what inspired me to become a scientist. Her incredible patience to answer my never-ending questions, our quiet moments looking through her telescope into the night sky trying to see different constellations, and so much more, shaped me as a female scientist. She did what she came here to do, and I recovered from my grief only to pick up where she left off- to devote the rest of my life to cancer care and research.

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