

**Monte Carlo Modelling of Tumour
Growth, Hypoxia and Radiotherapy
in Head and Neck
Squamous Cell Carcinoma**

Wendy M. Harriss

*A report submitted for acceptance
as a thesis for the degree of
Doctor of Philosophy
from the School of Chemistry and Physics
University of Adelaide, South Australia, Australia*

September 2011

Table of Contents

I. LIST OF FIGURES.....	i
II. LIST OF TABLES.....	xi
III. ABBREVIATIONS.....	xv
IV. ABSTRACT.....	xvii
V. STATEMENT OF AUTHENTICITY.....	xxi
VI. ACKNOWLEDGEMENTS.....	xxiii
VII. PUBLICATIONS & PRESENTATIONS.....	xxv
CHAPTER 1. INTRODUCTION.....	1
1.1. HEAD AND NECK SQUAMOUS CELL CARCINOMA OVERVIEW.....	1
<i>1.1.1. Disease Outline.....</i>	<i>1</i>
<i>1.1.2. Tumour Hypoxia.....</i>	<i>2</i>
<i>1.1.3. Treatment of Head and Neck Squamous Cell Carcinoma.....</i>	<i>3</i>
1.1.3.1. Treatment Modalities and Strategies	
1.1.3.2. Current Radiotherapy Prognosis	
1.2. RADIO THERAPY RESPONSE PREDICTION USING COMPUTER MODELLING.....	6
<i>1.2.1. The Need for Computer Models</i>	<i>6</i>
<i>1.2.2. The Use of Models for Predicting Radiotherapy Outcome</i>	<i>7</i>
1.2.2.1. The Monte Carlo Modelling Technique	
1.3. AIMS OF THE CURRENT STUDY	8
1.4. THESIS OUTLINE.....	10

CHAPTER 2. AN OVERVIEW OF HEAD AND NECK CANCER

RADIOBIOLOGY	13
2.1. BIOLOGY OF HEAD AND NECK SQUAMOUS CELL CARCINOMA.....	13
2.1.1. <i>Head and Neck Anatomy</i>	13
2.1.2. <i>Head and Neck Squamous Cell Carcinoma Biology</i>	14
2.1.2.1. Carcinogenesis of HNSCC	
2.1.2.2. Tumour Hypoxia in HNSCC	
2.2. TUMOUR RADIOBIOLOGY OVERVIEW.....	20
2.2.1. <i>Introduction</i>	20
2.2.1.1. Radiation Induced Cell Death	
2.2.1.2. Relative Biological Effectiveness	
2.2.1.3. The 5 R's of Radiobiology	
2.2.2. <i>Tumour Hypoxia in HNSCC Radiotherapy</i>	26
2.2.2.1. The Oxygen Enhancement Ratio	
2.2.2.2. Hypoxia and Tumour Control in HNSCC Radiotherapy	
2.2.3. <i>Accelerated Repopulation in HNSCC Radiotherapy</i>	29
2.2.4. <i>Fractionating Radiotherapy Treatment</i>	31
2.2.4.1. Aims and Techniques	
2.2.4.2. HNSCC Clinical Trial Review	

CHAPTER 3. A REVIEW OF TUMOUR GROWTH, HYPOXIA AND

RADIOTHERAPY MODELLING	35
3.1. INTRODUCTION.....	35
3.2. THE MONTE CARLO TECHNIQUE.....	37
3.3. MODEL OUTLINES	39
3.3.1. <i>Analytical Tumour Models</i>	39
3.3.2. <i>Stochastic Tumour Models</i>	43
3.3.2.1. Early Models	
3.3.2.2. Recent Models	
3.4. SUMMARY	53

CHAPTER 4. MODELLING TUMOUR GROWTH.....	59
4.1. INTRODUCTION.....	59
4.2. BIOLOGICAL MECHANISMS AND MODEL PARAMETERS IN THE TUMOUR GROWTH ALGORITHM.....	60
4.2.1. <i>Modelling Cell Division and Epithelial Cell Hierarchy.....</i>	60
4.2.2. <i>Cellular Oxygenation.....</i>	64
4.2.2.1. The Distribution of Oxygen	
4.2.2.2. Applying Oxygen Values to the Cell Population	
4.2.2.3. The Effect of Oxygen on the Cell Cycle	
4.2.2.4. Hypoxia Induced Cell Quiescence and Death	
4.2.3. <i>Limitations and Assumptions.....</i>	69
4.2.4. <i>Parameter Summary.....</i>	70
4.3. ALGORITHM DESIGN AND ANALYSIS METHODS.....	72
4.3.1. <i>Programming Methods.....</i>	72
4.3.1.1. Monte Carlo Based Parameter Assignment	
4.3.1.2. Programming Tools	
4.3.1.3. The Linked List Method of Data Management and Model Efficiency	
4.3.2. <i>The Tumour Growth Algorithm Work Flow</i>	74
4.3.3. <i>Tumour Growth Model Implementation.....</i>	74
4.3.3.1. Parameter Input	
4.3.3.2. Simulation Output Analysis	
4.3.3.3. Computer System Requirements	
4.3.3.4. Analysis and Statistical Methods	
4.4. TUMOUR GROWTH ALGORITHM PARAMETER ANALYSIS.....	78
4.4.1. <i>Cell Kinetics of Oxic and Hypoxic Tumours.....</i>	78
4.4.1.1. Stem Cell Division	
4.4.1.2. Transit Cell Division	
4.4.1.3. Cell Cycle Time and Cell Death	
4.4.2. <i>Oxygen Distribution Effects.....</i>	84
4.4.3. <i>Random Seed Number Effects</i>	86
4.5. TUMOUR GROWTH ALGORITHM CONCLUSIONS.....	88

CHAPTER 5. MODELLING OF THE EFFECTS OF	
CONVENTIONALLY FRACTIONATED RADIOTHERAPY.....	91
5.1. INTRODUCTION.....	91
5.2. MECHANISMS AND PARAMETERS IN THE RADIATION EFFECT	
ALGORITHM.....	92
5.2.1. <i>Modelling of Radiation Induced Cell Death.....</i>	<i>92</i>
5.2.1.1. Linear Quadratic Cell Kill	
5.2.1.2. Oxygenation Dependent Cell Kill	
5.2.2. <i>Modelling Reoxygenation.....</i>	<i>95</i>
5.2.2.1. Reoxygenation Algorithm Development	
5.2.2.2. Onset Time of Tumour Reoxygenation: an Experimental Study	
5.2.3. <i>Modelling of Accelerated Repopulation during Radiotherapy.....</i>	<i>118</i>
5.2.4. <i>Radiation Effect Model Parameter Summary</i>	<i>119</i>
5.2.4.1. Parameters Values and Ranges	
5.2.4.2. Assumptions and Limitations	
5.3. RADIATION EFFECT ALGORITHM DEVELOPMENT	121
5.3.1. <i>Implementing Efficient Randomised Cell Kill.....</i>	<i>121</i>
5.3.2. <i>Algorithm Workflow.....</i>	<i>122</i>
5.3.3. <i>Radiotherapy Algorithm Analysis Methods.....</i>	<i>124</i>
5.3.3.1. Output Results Format	
5.3.3.2. Data and Statistical Analysis Methods	
5.3.3.3. Model Validation Methods	
5.4. RADIATION EFFECT ALGORITHM RESULTS AND DISCUSSION.....	126
5.4.1. <i>Results Interpretation and Parameter Analysis.....</i>	<i>127</i>
5.4.1.1. Results Interpretation based on Cell Type	
5.4.1.2. The Level of Cell Kill Required for Tumour Control	
5.4.1.3. Statistical Variations due to the Random Seed Number	
5.4.1.4. Oxic Tumour Model Outcomes	
5.4.1.5. Hypoxic Tumour Outcomes	
5.4.1.6. Comparison of Oxic and Hypoxic Tumour Results	
5.4.1.7. Results Summary	

5.4.2.	<i>Validation of the HYP-RT Model</i>	147
5.4.2.1.	Comparison to Linear Quadratic Theory	
5.4.2.2.	Comparison to Clinical Trial Data	
5.5.	RADIATION EFFECT ALGORITHM CONCLUSIONS.....	152

CHAPTER 6. MODELLING ALTERED FRACTIONATION

RADIOTHERAPY	155	
6.1.	INTRODUCTION.....	155
6.2.	MODELLING ALTERED FRACTIONATION SCHEDULES.....	157
6.2.1.	<i>Radiotherapy Schedule Selection</i>	157
6.2.2.	<i>Simulation Methods</i>	159
6.2.3.	<i>Model Outcome Analysis Methods</i>	159
6.3.	ALTERED FRACTIONATION RESULTS AND DISCUSSIONS.....	162
6.3.1.	<i>Total Dose, Fraction Number and Treatment Time Outcomes</i>	162
6.3.1.1.	Hypoxic Tumours	
6.3.1.2.	Oxic Tumours	
6.3.1.3.	Comparison of Oxic and Hypoxic Tumours	
6.3.1.4.	Impact of Dose per Fraction Dependent OER Curves	
6.3.2.	<i>Ranking of Normal Tissues Effects Based on Calculated BED</i>	172
6.3.2.1.	Oxic and Hypoxic Tumour BED Rankings	
6.3.2.2.	Calculated BED versus Clinical Trial Toxicities	
6.3.3.	<i>Comparison of Model Predictions with Clinical Trial LC Data</i>	179
6.3.3.1.	Method 1: Assessing the Percentage of Controlled Tumours while Varying the Random Number Seed	
6.3.3.2.	Methods 2: Using Poisson Theory to Calculate TCP from Averaged Cell Survival	
6.4.	CONCLUSIONS.....	183

CHAPTER 7. MODELLING NEW ALTERED RADIOTHERAPY

SCHEDULES	187
7.1. INTRODUCTION.....	187
7.2. NEW FRACTIONATION SCHEDULES.....	187
7.1.1. <i>Fractionation Design</i>	187
7.1.2. <i>Schedule Implementation and Analysis Methods</i>	189
7.3. NEW SCHEDULE MODELLING RESULTS AND DISCUSSIONS.....	190
7.1.3. <i>Total Modelled Doses required for Tumour Control</i>	190
7.1.3.1. Oxidic Tumour Simulations	
7.1.3.2. Hypoxic Tumour Simulations	
7.1.4. <i>Ranking of Normal Tissue Effects Based on Calculated BED</i>	192
7.1.4.1. Oxidic Tumour BED Results	
7.1.4.2. Hypoxic Tumour BED Results	
7.1.4.3. The Effects of Modelling a Constant versus Variable OER Curve	
7.4. CONCLUSIONS.....	199
 CHAPTER 8. FINAL CONCLUSIONS	203
8.1. MODEL DEVELOPMENT SUMMARY	203
8.2. MODEL RESULTS SUMMARY	206
8.3. FUTURE DIRECTIONS	212
 APPENDIX	215
A:	215
B:	221
C:	227
 REFERENCE LIST	231

I. LIST OF FIGURES

Figure 2.1. A cross sectional illustration of the human head and neck region displaying many of the constituent sites affected by squamous cell carcinoma (www.macmillan.org.uk).

Figure 2.2. Epithelial non-keratinised stratified squamous cell structure (Henrikson 1997).

Figure 2.3. Carcinogenesis of carcinomas from a single mutated cell to a malignant and invasive tumour (Le 2004, Hall 2006).

Figure 2.4. Development of hypoxia in tissue, comparing chronic hypoxia which arises due to limited oxygen diffusion, with acute hypoxia arising from temporarily non-functioning blood vessels (Brown 1990, Hall 2006).

Figure 2.5. Human in vivo Eppendorf tumour oxygenation (pO_2) measurement data from HNSCC patients prior to radiotherapy (adapted from pO_2 data reported from the references provided in the legend).

Figure 2.6. The four main phases of the cell cycle starting with the first gap phase (G1), followed by the DNA synthesis phase (S), the second gap phase (G2), and with completion in the Mitosis phase (M).

Figure 2.7. An illustration of two ionising radiation cell damage processes with DNA as the target (Hall 2006). The indirect process involves liberation of an atomic electron which then reacts, producing highly reactive free radicals that can cause DNA damage. With oxygen present, this damage is “fixed”. Other damage mechanisms are also shown which involve liberation of an electron followed by direct DNA damage.

Figure 2.8. The oxygen enhancement ratio of irradiated cells of increasing oxygenation (pO_2) for the conventional (2 Gy) dose per fraction and for decreasing dose per fraction (Dasu 1998, 1999, Kirkpatrick 2004).

Figure 2.9. The fractionation effect on cell survival in Radiotherapy, where four dose fractions are compared to a single dose fraction (Dasu 1998, 1999, Kirkpatrick 2004).

Figure 4.1. The epithelial cell proliferative hierarchy used in the model, outlining the different cell types modelled, and the daughter cell products of these cell types upon division.

Figure 4.2. The probability distributions used for cell cycle time allocation in the model for transit and stem cells. The “Stem total” curve represents the overall lifetime probability of stem cells which first undergo a resting G0 phase followed by a cell cycle.

Figure 4.3. The distribution of oxygen levels used to simulate moderate and severe tumour hypoxia and oxic tumours, compared to published data. The modelled distributions represent the pO_2 histograms outputs from the model using a log-normal, normal or uniform random number probability distribution of pO_2 values to allocate cellular oxygenation.

Figure 4.4. The CCT adjustment factor used to increase the duration of the cell cycle with decreasing pO_2 , adapted from published data and fitted to an exponential curve (Alarcon 2004).

Figure 4.5. An outline of the HYP-RT tumour growth algorithm, where a single stem cell is propagated up to tumour consisting of 10^8 cells. The “Cellarray” is the cell storage vector and “cellmax” is the final number of cells.

Figure 4.6. The graphical user interface, developed in the Java programming language to enable simple tumour and treatment related parameter value setting, and the initiation of multiple “batch” runs iterating over different random seed numbers and parameter values.

Figure 4.7. a) The average percentages of cell types within simulated tumours of 10^8 cells for a variety of Spercent values between 2% and 30%, and b) oxic versus moderately hypoxic tumour cell types in the population using an Spercent value of 3%.

Figure 4.8. Simulation results of a) tumour doubling times (T_D), and b) total tumour growth times, varying the stem cell symmetrical division probability (Spercent) for oxic and moderately hypoxic tumours up to 10^8 cells. Note that the error bars in a) were smaller than the scale used.

Figure 4.9. Oxic tumour growth curves for a range of stem cell symmetrical division probabilities (Spercent).

Figure 4.10. Hypoxic tumour growth curves for a range of stem cell symmetrical division probabilities (Spercent).

Figure 4.11. Oxic tumour doubling times (T_D) throughout growth, varying the stem cell symmetrical division probability (Spercent).

Figure 4.12. Hypoxic tumour doubling times (T_D) throughout growth, varying the stem cell symmetrical division probability (Spercent).

Figure 4.13. The stem cell percentages in simulated tumours of three oxygenation levels, varying the stem cell symmetrical division probability (Spercent) from 2%, up to the maximum possible value of 30% (the latter is applicable during accelerated repopulation). Note that the standard deviations are not visible on this scale.

Figure 4.14. Tumour growth and doubling times (T_D) for three different tumour oxygenation levels. Note that there is no data for hypoxic tumours for Spercent = 1% because of a lack of tumour growth using this value.

Figure 4.15. The impact of the hypoxia induced quiescent cell percentage on tumour doubling times (T_D), controlling the number of cells that cease to cycle when their pO_2 value fall to 1 mm Hg.

Figure 4.16. Oxic tumour doubling times (T_D) for five different random seed numbers, showing the change in T_D over the entire period of growth. The Spercent stem cell parameter was held constant at 3%.

Figure 4.17. Hypoxic tumour doubling times (T_D) for five different tumour random seed numbers, showing the change in T_D over the entire period of growth. The Spercent stem cell parameter was held constant at 3%.

Figure 5.1. a) Oxygen enhancement ratio (OER) curves implemented in the model for adjusting the radiosensitivity of cells during radiotherapy, based on cellular pO_2 and dose per fraction (Dasu 1998, 1999, Kirkpatrick 2004), and b) conversion of the OER curves into a cell death probability function.

Figure 5.2. The irradiation and pO_2 measurement schedule for the tumour xenografts ($n=42$), where pO_2 measurements were performed after 0, 3, 9, 20, 30 or 40 Gy in 20 mice, with the remaining xenografts used in immunohistochemical hypoxia staining work.

Figure 5.3. a) the animal irradiation tray and a $2 \times 35 \text{ cm}^2$ radiation field aligned over the pelvis and hind leg, for a group of mice in restraining bags with adjacent wax bolus, and b) the plastic heat pressed bag used for animal restraint during radiotherapy. The plastic was perforated to prevent perspiration build up and overheating, and pinned to the tray during irradiation.

Figure 5.4. The OxyLab system fibre optic probe manufactured Oxford Optronix Ltd ($230 \mu\text{m}$ width shaft and $280 \mu\text{m}$ tip diameter) used for in vivo pO_2 measurement.

Figure 5.5. The set up of the mouse and hind leg FaDu xenograft for OxyLab pO_2 probe measurements using a micromanipulator, with the probe entering the tissue in the inferior to superior direction.

Figure 5.6. A transverse slice and Pinnacle³ TPS isodose curves (6 MV x-ray beam from a 6/100 Varian linear accelerator) for three mice, set up in the irradiation position, indicating the 95% and 100% isodose curves and the approximate tumour positions.

Figure 5.7. Preliminary experiment tumour diameter and volume, during 15 days of tumour growth (grey, $n=12$, 2 diameter measurements per tumour), followed by five daily fractions of 3 Gy irradiation starting at day 15 ($n=9$).

Figure 5.8. Average change in tumour volume ($n=40$) during radiotherapy starting 8 days after xenograft cell injection (note that animal numbers reduced to 10 by day 19 due to elimination of mice proceeding pO_2 measurements). Two control tumours received no irradiation and were left to grow until day 15. No treatment occurred on days 13 and 14 because of the weekend break.

Figure 5.9. Oxygenation measurements indicating, a) a significant increase in pO_2 with increasing dose of fractionated radiotherapy from 0 to 30 Gy to 40 Gy ($p < 0.05$), and b) no significant difference between the periphery, centre and total average pO_2 of the tumours.

Figure 5.10. Plots for a) oxygenation data (pO_2) for small, medium and large tumours ($n=10$, $n=9$, $n=1$, with up to 12 points measured per tumour), b) the ranges of tumour volumes within each volume group.

Figure 5.11. A comparison of the pO_2 readings after 2 and 5 minutes, for all mice involved in the OxyLab procedure ($n=20$), with an average of six points measured per tumour and three tumours per dose group from 0 to 40 Gy, for a) all 2 minute data compared to all 5 minute data, and b) the plot of the 2 minute vs. the 5 minute measurements corresponding to each tumour point (96 pairs of measurements).

Figure 5.12. Analysis of a selection of immunohistochemical cross sections of a sample of tumours receiving, a) 0 Gy, b) 0 Gy, c) 1x3 Gy, d) 3x3 Gy, e) 5x3+3x5 = 30 Gy, and f) 5x3+5x5 = 40 Gy. Fluoroscopic imaging shows the hypoxic green cells (Pimonidazole hypoxia marker), red endothelial/vessel cells and blue proliferating cells. Note that xenograft B grew for an extended 15 day period before excision of the tumour, hence the larger volume of the tumour.

Figure 5.13. The relative percentage of green hypoxic cells using Pimonidazole compared to all stained cell pixels (including red vessel and blue proliferating cell pixels, based on the Immunohistochemical staining tumour cross sectional images of 17 tumours receiving between 0 and 40 Gy, plotted against a) tumour volume, and b) total dose.

Figure 5.14. The relationships among the relative percentage of the green hypoxic cells, red vessel cells and blue proliferating cells and pixel count with total dose or tumour volume, in 17 immunohistochemical stained xenografts cross-sections.

Figure 5.15. The percentages of red, green and blue pixels (representing vessel cells, hypoxic cells and proliferating cells) in order of smallest to largest tumour volume (tumour received between 0 and 45 Gy) in 17 immunohistochemically stained xenograft cross sections, excluding tumours with folding artefacts in the $7 \mu m$ and with tumour volumes less than $15 mm^3$.

Figure 5.16. A flow diagram of the radiation effect algorithm, where initiation of treatment is followed by continual cell growth between subsequent treatment fractions. Accelerated repopulation is initiated once, and reoxygenation “events” are initiated and then repeated until the tumour is fully oxygenated. Treatment is complete when either the number of desired fractions has been delivered or total cell death has occurred.

Figure 5.17. Comparison of the number of 2 Gy fractions required in the HYP-RT model to kill all “basal” or all “stem” cells compared to the linear quadratic (LQ) model in which the cell population is reduced to less than 1 cell (the first fraction that achieves <1.000 cells remaining), for oxic tumour conventional radiotherapy.

Figure 5.18. The increased doses per fraction (d/#) required during conventional radiotherapy of oxic tumours to account for accelerated repopulation (AR), assuming a fixed total treatment time of 6 weeks and the increase in d/# coinciding with the onset of AR, for various onset times of AR and AR boost factors . A dotted line is shown at the standard 2 Gy/# level.

Figure 5.19. The number of conventional radiotherapy fractions required to model 100% TCP in oxic tumours, varying the AR boost factor from 3 to 15 in a) a column graph, and b) in a plot of fraction number versus AR onset time. Note that treatment simulations with no AR considered took 6 weeks of tumour time (30 fractions).

Figure 5.20. Cell survival curves of two oxic virtual tumours undergoing conventional radiotherapy, simulating no onset of AR and onset of AR at 2 weeks into treatment.

Figure 5.21. The increased doses per fraction (d/#) required during conventional radiotherapy of hypoxic tumours to account for accelerated repopulation (AR), assuming a fixed total treatment time of 8 weeks and the increase in d/# coinciding with the onset of AR, for various onset times of AR and AR boost factor values . A dotted line is shown at the standard 2 Gy per fraction level.

Figure 5.22. The increased doses per fraction (d/#) required during conventional radiotherapy of hypoxic tumours to account for accelerated repopulation (AR), assuming a fixed total treatment time of 8 weeks and the increase in d/# coinciding with the onset of AR, for various onset times of AR and ROx. A dotted line is shown at the standard 2 Gy per fraction level.

Figure 5.23. A comparison of the average number of conventional radiotherapy fractions required for moderately hypoxic tumours with no reoxygenation (ROx), varying the onset of accelerated repopulation (AR) and AR boost factor from a) 3 to 15, and b) from 7 to 15 in a plot of fraction number vs. AR onset time. A dotted line represents the standard number of fractions for the case of no AR and no ROx.

Figure 5.24. A comparison of the average number of conventional (2 Gy) radiotherapy fractions required for cell kill and the timing of full tumour reoxygenation (ROx) for moderately hypoxic tumours, varying the half life of hypoxia induced cell quiescence, with ROx onset at the start of treatment.

Figure 5.25. Oxygenation histograms after fractions of conventional radiotherapy (fraction 1 to 8 only) for a moderately hypoxic tumour, with reoxygenation (ROx) initiated four hours after each dose fraction.

Figure 5.26. A comparison of the average number of conventional radiotherapy fractions required for moderately hypoxic tumours, with increasing reoxygenation (ROx) onset times, with no accelerated repopulation considered.

Figure 5.27. The number of treatment fraction required to model 100% TCP for moderately hypoxic tumour conventional radiotherapy, varying the onset times of accelerated repopulation (AR) and reoxygenation (ROx). A dotted line represents the standard number of fractions for the case of no AR and no ROx.

Figure 5.28. Cell survival curves from simulations of conventional radiotherapy of moderately hypoxic tumours, varying the onset times of accelerated repopulation (AR) and reoxygenation (ROx).

Figure 5.29. The relative influences of accelerated repopulation (AR) on oxic and moderately hypoxic tumour simulations, for various onset times of AR and using the default AR boost factor of 10.

Figure 5.30. A comparison of the average number of radiotherapy fractions required for severely hypoxic and moderately hypoxic tumours for onset times of accelerated repopulation (AR) and reoxygenation (ROx) of between 0 to 2 weeks.

Figure 5.31. The effects of moderate, severe and extreme hypoxia on tumour control, varying the onset times of accelerated repopulation (AR) and reoxygenation (ROx), outlining the combination for which extreme hypoxia required an increased dose.

Figure 6.1. The number of fractions simulated to achieve 100% tumour control probability (TCP) in the model for hypoxic tumours for 11 fractionation schedules (Table 6.1), compared to the number of fractions delivered in clinical trials.

Figure 6.2. The total doses simulated to achieve 100% tumour control probability (TCP) in the model for hypoxic tumours for 11 fractionation schedules (Table 6.1), compared to the number of fractions delivered in clinical trials.

Figure 6.3. The total doses simulated to achieve 100% tumour control probability (TCP) in the model, based on stem cell elimination only for hypoxic tumours for 11 fractionation schedules (Table 6.1), compared to the number of fractions delivered in clinical trials.

Figure 6.4. Total dose requirements in the model to achieve 100% TCP, for the elimination of all stem cells versus the elimination of all “basal” cells which includes all stem, transit and level 1 differentiating cells, for 11 fractionations schedules (Table 6.1).

Figure 6.5. Cell survival curves throughout treatment from simulations of 8 different fractionation schedules (Table 6.1), with onset of accelerated repopulation (AR) at 2 weeks and onset of ROx at 0 weeks.

Figure 6.6. The total doses simulated to achieve 100% TCP in the model for oxic tumours for 11 fractionation schedules (Table 6.1), compared to the number of fractions delivered in clinical trials.

Figure 6.7. The total doses simulated to achieve 100% TCP in the model for oxic versus hypoxic tumours, varying the onset of AR for 11 fractionation schedules. No reoxygenation (ROx) was implemented during these simulations.

Figure 6.8. Total treatment times required to achieve 100% TCP in the model for 11 fractionation schedules with various onset times of accelerated repopulation (AR), for a) oxic tumours, and b) hypoxic tumour simulations. No reoxygenation (ROx) was implemented for these simulations.

Figure 6.9. The effects on total dose required for 100% TCP when modifying the OER curve with dose per fraction compared to modelling one fixed OER curve with a maximum value of 3.0, during simulations of 8 various fractionation schedules (Table 6.1) for various onset times of accelerated repopulation (AR) and reoxygenation (ROx).

Figure 6.10. Rankings of acute normal tissue biological effective doses (BED) based on the total dose required for 100% for 11 fractionation schedules in a) oxic tumours, and b) hypoxic tumour simulations (in both cases the lowest BED ranking is optimal for acute normal tissue effects).

Figure 6.11. Late reacting normal tissue biological effective dose (BED) rankings based on the total dose required for 100% TCP for 11 fractionation schedules (Table 6.1), for a) oxic tumours, and b) hypoxic tumour simulations (in both cases the lowest ranking is optimal for late normal tissue effects).

Figure 6.12. Comparisons of tumour control probability (TCP) using a) a zero cell threshold and b) a five cell threshold with varying accelerated repopulation (AR) and reoxygenation (ROx) onset times and corresponding clinical trial fraction numbers for 11 schedules with reported clinical trial local control (LC) percentages.

Figure 6.13. Comparisons of tumour control probability (TCP) using modelled cell kill data and Poisson theory for varying AR and ROx onset times and corresponding clinical trial fraction numbers for 11 schedules with reported clinical trial local control (LC) percentages.

Figure 7.1. Oxic tumour simulations with varying onset times of AR comparing the total doses required for 100% tumour control probability (TCP) for four new altered fractionation schedules and five clinical trial schedules.

Figure 7.2. Hypoxic tumour simulations varying the onset times of AR and ROx comparing the dose required for 100% tumour control probability (TCP) for four new altered fractionation schedules and five clinical trial schedules.

Figure 7.3. BED calculations based on the modelled 100% TCP dose, for predictions of a) acute normal tissue effects and b) late normal tissues effects in oxic tumour simulations for four new and five clinically trialled schedules and various onset times of AR. The red circles indicate the worst schedules and the green circles the most beneficial schedules in terms of the predicted a) acute and b) late normal tissue tolerances.

Figure 7.4. BED calculations based on the modelled 100% TCP dose, for predictions of a) acute normal tissue effects and b) late normal tissues effects in moderately hypoxic tumour simulations for four new and five clinically trialled schedules and various onset times of accelerated repopulation (AR) and reoxygenation (ROx). The red circles indicate the worst schedules and the green circles the most beneficial schedules in terms of the predicted a) acute and b) late normal tissue tolerances.

Figure 7.5. Total doses for the specific case of onset of accelerated repopulation (AR) at 2 weeks and onset of reoxygenation (ROx) at 0 weeks, for hypoxic tumour simulations for four new and five clinically trialled schedules modelling a fixed versus variable OER curve (dependent on dose per fraction).

Figure 7.6. BED calculations for predictions of acute and late normal tissue tolerances for the specific case of onset of accelerated repopulation (AR) at 2 weeks and onset of reoxygenation (ROx) at 0 weeks, for hypoxic tumour simulations for four new and five clinically trialled schedules, modelling a fixed vs. variable OER curve (dependent on dose per fraction).

II. LIST OF TABLES

Table 4.1. The modelled percentages of cells in four commonly reported pO_2 ranges based on published tumour oxygenation histogram data.

Table 4.2. The key parameters in the tumour growth algorithm of the HYP-RT model.

Table 4.3. The impact of the hypoxia induced quiescent cell half life on tumour growth and stem cell percentage.

Table 5.1. The percentages of cells, P_k , affected during reoxygenation “events” in the model, where k is the number of increments of 3 mm Hg allocated to the cells to increase their oxygenation attributes based on Binomial theory.

Table 5.2. OxyLab pO_2 measurement data for all tumour points analysed. Up to six points were analysed per tumour, with data recorded at 2 and 5 minutes after probe insertion, per point. The total mouse number used was 20 and the total number of readings recorded was 193.

Table 5.3. Modelling parameters used in the fractionated radiotherapy effect algorithm, including parameter values/ ranges and literature references where applicable.

Table 5.4. The number of fractions difference required in simulations to eliminate all cells compared to 1 cell remaining and all cells compared to 5 cells remaining (killing all stem+transit+level 1 differentiating “basal” cells or all stem cells only), averaged over multiple simulations of moderately hypoxic tumours with different onset times of accelerated repopulation and reoxygenation.

Table 5.5. Comparison of the HYP-RT and linear quadratic (LQ) models in terms of the number of 2 Gy fractions required for 100% tumour control probability (TCP) or the first occurrence of less than 1,000 cell survival, respectively, including the effects of accelerated repopulation (AR) and with a “q” value representing the dose modification factor due to low oxygenation in the LQ model.

Table 6.1: The 11 HNSCC clinical trial schedules simulated with the HYP-RT model. Schedules 2-8 are from therapeutically beneficial trials, schedules 9-10 are from trials with no therapeutic gain, and schedule 11 is one in which a two week break has been inserted to simulate patient recovery time due to acute effects.

Table 6.2: Rankings of calculated BBED acute and late normal tissue effects of 11 fractionation schedules for oxic tumour simulations, where a high number indicates a worse ranking and a low number indicates a better ranking of predicted normal tissue toxicity levels.

Table 6.3: Rankings of calculated BBED acute and late normal tissue effects of 11 fractionation schedules for hypoxic tumour simulations, where a high number indicates a worse ranking and a low number indicates a better ranking for predicted normal tissue toxicity levels.

Table 6.4: Summary of the overall order of schedules predicted to have to the lowest to highest normal tissue toxicity for acute and late effects for 11 fractionation schedules, averaged over a range of onset times of accelerated repopulation (AR) and reoxygenation (ROx).

Table 7.1. The four new altered fractionation schedules devised for efficacy analysis in the HYP-RT model.

APPENDIX A:

HNSCC clinical trials from the 1980's to the present, indicating the conventional and altered fractionation schedules used to treat the disease as the sole modality of treatment. Conventional treatment arms for all studies use 1.8 to 2 Gy per fraction, 1x5 fractions per week, in 7 to 8 weeks (unless otherwise indicated).

APPENDIX B:

i) Moderately hypoxic tumour conventional radiotherapy simulation cell kill results, in terms of the number of 2 Gy fractions required to achieve total “basal” (stem, transit and level 1 differentiating cell) and stem cell only elimination, for various reoxygenation (ROx) and accelerated repopulation (AR) onset times.

ii) Oxic tumour Conventional Schedule simulation total cell kill results in terms of the number of 2 Gy fractions required to achieve total “basal” (stem, transit and level 1 differentiating cell) and stem cell only elimination, for accelerated repopulation (AR) onset times, and alpha beta ratios

APPENDIX C:

i) Moderately Hypoxic tumour simulation cell kill results for the total elimination of all stem transit and level 1 differentiating cells, for various onset times of accelerated repopulation (AR) and reoxygenation (ROx). Schedule numbers can be referred to in Tables 6.1 and 7.1 of this report.

ii) Oxic tumour simulation cell kill results for the total elimination of all stem transit and level 1 differentiating cells, for various onset times of accelerated repopulation (AR). Schedule numbers can be referred to in Tables 6.1 and 7.1 of this report.

III. ABBREVIATIONS

AR	– accelerated repopulation
BED	– biological effective dose
CT	– computed tomography
DNA	– deoxyribonucleic acid
FHV	– Fractional hypoxic volume
Gy	– Gray = 1 Joule / Coulomb
HNSCC	– head and neck squamous cell carcinoma
HP	– hypoxic percentage (of cells in a tumour)
HYP-RT	– ‘Hypoxic Radiotherapy’ simulation model
IMRT	– intensity modulated radiotherapy
KeV	– kilo electron volt
KVp	– kilo voltage potential
LET	– linear energy transfer
LQ	– linear quadratic (theory of cell survival)
M	– molar
MV	– mega voltage (x-ray beam)
MeV	– mega electron volt
NTCP	– normal tissue complication probability
OER	– oxygen enhancement ratio
pO ₂	– partial pressure of oxygen
PTV	– planning target volume
RBE	– relative biological effectiveness
ROx	– reoxygenation (during radiotherapy)
RT	– radiotherapy
SCC	– squamous cell carcinoma
SF ₂	– surviving fraction of cells after 2 Gy irradiation
TCP	– tumour control probability
T _D	– tumour double time
T _{pot}	– potential tumour doubling time (equal to T _D when all cells are cycling clonogenic cells)

IV. ABSTRACT

Tumour hypoxia is the inadequate supply of oxygen in living tissue. Hypoxia is a major problem in the treatment cancer with ionising radiation because of the associated increase in radioresistance of hypoxic tumour cells. This effect can cause up to a three fold increase in the radiation dose required to kill the hypoxic cells compared to well oxygenated cells. Many locally advanced head and neck tumours exhibit hypoxia to some degree, and there is direct evidence that hypoxic tumour sub-volumes and their associated mean oxygenation levels have a direct influence on local tumour control after radiotherapy (Nordsmark 2005).

Currently, head and neck cancer radiotherapy local control rates lie at approximately 80% for early stage disease, but reduce significantly (often below 50%) for locally advanced tumours. Efforts to improve these statistics through dose and fractionation modifications in randomised clinical trials have been made in recent decades using alternate fractionation schedules, but the average prognosis has not improved significantly.

The effects of tumour reoxygenation during fractionated radiotherapy can assist in re-sensitising previously hypoxic tissue; however the complex dynamics and patient dependent characteristics of this phenomenon make the benefits difficult to quantify. Head and neck cancers, specifically head and neck squamous cell carcinoma (HNSCC), have also been shown to experience the phenomenon of accelerated repopulation during fractionated radiotherapy. Accelerated repopulation enhances cellular proliferation as a response to the trauma caused by treatment, and contributes to the low HNSCC local control rates after radiotherapy.

The modelling work developed for this report was undertaken to better understand the mechanisms and quantitative effects of HNSCC cellular kinetics and tumour oxygenation during growth and radiotherapy. The goal of individualising treatment planning for this disease was the motivation for developing the model. A key aim was to produce an end product to be used as an efficient and user-friendly radiobiological tool for the input on tumour specific properties such as tumour oxygenation and reoxygenation onset time, to investigate their effects on cell kill during radiotherapy.

To this end, a Monte Carlo model, named *HYP-RT* (for **HYP**oxic-**R**adio**T**herapy simulation), was developed. *HYP-RT* simulates the tumour cell division process according to epithelial proliferative hierarchy, starting from a single stem cell. Monte Carlo methods were used to simulate the probabilistic nature of the biological and radiobiological mechanisms and parameters incorporated into the model, e.g. the distribution of cell cycle times (normal or exponential) and oxygenation levels (normal or log-normal), and the randomised methods of cell kill and oxygenation increase during treatment. Probabilistic methods were also used to make decisions during cell division, as to the type of daughter cell products that would emerge after the division of a mother cell.

After the growth of a 10^8 cell tumour, an algorithm was developed to model the effects of fractionated radiotherapy. This algorithm was designed to simulate the oxygen dependent radiosensitivity of individual tumour cells, as well as the effects of gradual reoxygenation and accelerated repopulation (through loss of stem cell division asymmetry). Both reoxygenation and accelerated repopulation could be onset at varying times after the start of treatment. Experimental animal work using HNSCC (FaDu cell line) xenografts was undertaken during this research, and showed that reoxygenation occurred very late in an accelerated radiation schedule (40 Gy in 2 weeks), indicating the need to investigate a range of reoxygenation onset times in the model (0 to 3 weeks).

Dynamic cell data was stored in a pre-allocated vector (the *Cellarray*) containing just over 10^8 object elements, with each element representing one tumour cell. This enabled efficient random access to the data. Linked list methods were used to chronologically order cells in the *Cellarray* based on their times of division. Model efficiency was paramount during model development, to ensure convenient use of the model for the current work and potential future research. Using linked list methods, the goal of a one hour maximum computation time to grow and treat a tumour was successfully achieved.

The model source code was written with the FORTRAN 95 programming language (compiler v7.1.0, *Lahey Computer Systems Inc.*), within the Visual Studio (2003, *Microsoft Corporation*) framework. Two additional graphical user interface programs were developed using the JAVA programming language (Java SE Development Kit 6.17), to 1) read in and interpret tumour data files, and 2) allow for the input of key tumour parameters before a simulation (or batches of simulations) and iteration over multiple parameter sets.

Cellular data and key algorithm parameters were written out to file at regular intervals (1000 hours by default), during tumour growth and before and after every dose fraction during treatment, for retrospective analysis. This data included the tumour pO₂ distribution, the instantaneous tumour growth rate and the number of cells of various types comprising the tumour.

Simulation results showed that tumour growth rate was strongly dependent on the percentage of stem cells in the tumour (modelled to be approximately 1% during growth). Incorporating a “moderately” hypoxic oxygen distribution increased tumour doubling times significantly, from 37 days for oxic tumours up to 65 days for moderately hypoxic tumours. This was attributed to the effects of oxygen dependent cell cycle slowing, cellular quiescence and necrosis.

Simulated conventional radiotherapy (5x2 Gy/wk) required on average an extra 16 Gy in total to achieve tumour control for moderately hypoxic compared to well oxygenated tumours. The effects of both accelerated repopulation and reoxygenation significantly altered the total doses required for tumour control, with accelerated repopulation effects dominating model outcomes. Accelerated repopulation and reoxygenation were found to be dependent on one another, making simulations of every combination of onset time for each effect necessary during model analysis.

During accelerated repopulation, a dose per fraction of 2.5 to 3.0 Gy was required to control the extra cell growth in an otherwise 2 Gy per fraction schedule. This equated to an extra 5 Gy being required to maintain tumour control for every week that the onset accelerated repopulation was brought toward the start of treatment. The benefits of reoxygenation reduced as the time of onset was delayed, with +1 Gy required to maintain tumour control for every week that reoxygenation was delayed.

Conventional fractionation simulation results had good agreement with standard Linear Quadratic theory, for the dose required to control well oxygenated tumours. However, comparison results were mixed for more complex cases involving hypoxic tumours with and without accelerated repopulation. When modelling altered fractionation schedules, simulation outcomes in terms of the total doses required for tumour control, agreed well with the prescriptions from published clinical trials. The most beneficial schedule, based on predicted total dose as well as biological effective doses (BED's) calculations for normal tissues, was the 10x1.1 Gy/week schedule (Pinto *et al.* 1991). However, there were up to 30 Gy differences in total dose and BED results when simulating

specific sets of tumour parameters for the same radiation schedule, highlighting the need for individualisation of treatment planning to improve the therapeutic ratio.

Four newly designed altered schedules were also simulated with the *HYP-RT* model. Results showed that using a concomitant boost at the beginning, rather than at the end of treatment, or using a “less aggressive” continuous hyper-accelerated radiotherapy (CHART) schedule (compared to the UK CHART schedule) may have potential therapeutic benefits compared to existing clinical schedules. Altering the oxygen enhancement ratio (OER) curve based on dose per fraction for the altered fractionation schedules, changed model results significantly for hyperfractionated schedules (up to 20 Gy). This highlighted the critical nature of the OER curve in predictive radiobiological tumour models.

In summary, the current research has involved the development, analysis and use of an efficient Monte Carlo tumour growth and radiotherapy model (*HYP-RT*). The model simulates a biologically plausible epithelial cell hierarchy, a large number of individual cells, tumour hypoxia, and the dynamics of reoxygenation and accelerated repopulation during radiotherapy. The user can input the desired oxygen distribution to describe the degree of tumour hypoxia as well as and the times of onset of treatment related effects, among many other cellular parameters. The model provides quantitative results regarding the total dose required to control a tumour, for a given fractionation schedule and tumour parameter set. It is hoped that computer models such as *HYP-RT* will be used in the near future as a tool to aid in the individualisation of radiotherapy planning, based on specific tumour experimental/imaging information, to improve prognosis for patients with HNSCC.

V. STATEMENT OF AUTHENTICITY

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution, and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968. The author acknowledges that copyright of published works contained within this thesis resides with the copyright holder(s) of those works.

I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library catalogue, the Australasian Digital Theses Program (ADTP) and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Signed:.....

Dated:.....

VI. ACKNOWLEDGEMENTS

I wish to give thanks to the School of Chemistry and Physics at the University of Adelaide, in accepting me into their postgraduate research program, and awarding me a scholarship which enabled me to study full time during the initial years of my PhD candidature. I also thank the University of Adelaide for further financial support which assisted in my attendance at several conferences and for the purchase of computer and experimental work equipment. Thank you to Dr Judith Pollard for your many years of dedicated work as the post-graduate Medical Physic program coordinator.

I am extremely grateful to have been accepted and welcomed into the Department of Medical Physics at the Royal Adelaide Hospital, and would like to whole-heartedly thank my supervisors Associate Professor Eva Bezak, Chief Medical Physicist, and Professor Eric Yeoh, Director of Radiation Oncology, for the their years of assistance, patience and support.

Eva, you have treated me with respect and kindness and have always given me your time when I have needed it, despite you very hectic schedule! I appreciate your efforts and consider working and studying with you an honour. I have very much enjoyed my time studying under your guidance, right from our first meeting at the beginning of my honours year in 2003.

Professor Yeoh, your support towards the Department of Medical Physics, and to post-graduate students is so very much appreciated. Thank you for your clinical guidance during my PhD research and for all of the wonderful editing work! I also appreciate your help in terms of financial support which assisted in funding my attendance at multiple conferences and workshops, as well as for these equipment needed for the animal experiments component of my research.

I would like to give kind thanks to Associate Professor Loredana Marcu, Senior Medical Physicist at the Royal Adelaide Hospital, for helping me to choose the direction of my research, for her kind support, and for her radiobiological knowledge which has assisted me greatly. Thanks also go to Professor Tim van Doorn and Dr Judith Pollard, for their supervision and guidance in the early years of this work.

Appreciation goes to all of the people that I have collaborated with, especially during the multi-disciplinary phase of animal experimental work, which was a new and exciting challenge for me. Thank you to Dr Tina Lavranos and Mrs Donna Fenu for their animal handling and cell line expertise, Dr Carlene Cullinane for the FaDu cell line donation, Professor Albert van der Kogel for the immunohistochemical imaging assistance, Mr Jim Manavis for tumour excise and cross-section advice and preparation, IMVS staff for animal handling and anaesthetic advice, Professor Cathy Malcontenti-Wison and Dr Peter Wong for *OxyLab* system assistance and equipment loan, and Mr Maarten Hermans, who joined the department as part of his masters work from the Technical University, Eindhoven in the Netherlands, for his willing assistance and friendship during many hours of animal preparation and irradiation.

The Department of Medical Physics at the Royal Adelaide Hospital has been a welcoming and positive environment to study, with all team members showing me support and kindness during my candidature. Kind thanks go to the whole team and especially to Christine Robinson for her administrative assistance and caring friendship which has (and continues to) mean a great deal to me.

The love and support of my family, Lesley, John and Laura, my Grandparents, and my dear husband Dr Damien Phillips, have helped me immensely during my years of study. Thank you my family, your love has helped me to remain calm, focussed and remember what really matters in life. Damien, you have helped me more than I can put into words. You have assisted me emotionally and technically in achieving my goals for the model and getting to the finishing line of this long but extremely rewarding project. Thank you from the bottom of my heart for all that you do for me, for sharing your programming skills, for your patience, and most of all for your unconditional love.

VII. PUBLICATIONS & PRESENTATIONS

Publications in refereed journals

- Harriss-Phillips W. M., Bezak E., Yeoh K. (2011), *Monte Carlo radiotherapy simulations of accelerated repopulation and reoxygenation for hypoxic head and neck cancer*. Br J Radiol. **84** 903–918.
- Harriss W.M., Bezak E., Yeoh K., Hermans M. (2010), *Measurement of reoxygenation during fractionated radiotherapy in head and neck squamous cell carcinoma xenografts*. Australas Phys Eng Sci Med. **33** 251-63.
- Tuckwell W.M., Bezak E., Yeoh K., Marcu L.(2008), *Efficient Monte Carlo modelling of individual tumour cell propagation for hypoxic head and neck cancer*. Phys Med Biol. **53** 4489-507. (Note: published in my former name of W. M. Tuckwell).
- *Awarded the status of one of the top 20 articles in Phys Med Biol in 2008*

Published book chapters

- Harriss W. M. (2011), *Radiobiological modelling of tumour hypoxia and radiotherapy*. Recent Advances and Research Updates: Medical Physics. [ISSN 0972-4699] Chapter 16, 257-278.

Papers in preparation

- Harriss-Phillips W. M., Bezak E., Yeoh K. *Development of a radiobiological Monte Carlo model of hypoxic head and neck cancer and radiotherapy, HYP-RT*. To be submitted to Computational and Mathematical Methods in Medicine.

- Marcu L.M., Harriss-Phillips W.M., *In silico* modelling of tumour response to treatment: current status. To be submitted as a review paper to Computational and Mathematical Methods in Medicine.

Conference oral and poster presentations

International

- Harriss W.M., Bezak E., Yeoh K. (2009), *Computer and tumour xenograft modelling: dynamic hypoxia in head & neck radiotherapy*. Poster presentation. World Congress on Medical Physics and Biomedical Engineering. Munich, Germany.
- Tuckwell W.M., Bezak E., Yeoh K. (2008), *Monte Carlo Modelling of Hypoxic Head and Neck Squamous Cell Carcinoma and Radiotherapy*. Oral presentation. European Society for Therapeutic Radiology and Oncology Conference. Barcelona, Spain.

National

- Harriss-Phillips W.M., Bezak E., Yeoh K. (2011), *Observation of Hypoxia in HNSCC Xenografts during Fractionated Radiotherapy*. Oral presentation. Engineering and Physics Sciences in Medicine Conference. Darwin, Australia.
- *Awarded best Radiobiology proffered paper by Keynote speaker, Professor Wolfgang Dorr*
- Harriss-Phillips W.M., Bezak E., Yeoh K. (2011), *Simulations of Hypoxic HNSCC with Clinical Trial and New Radiotherapy Schedules using the HYP-RT model*. Oral presentation. Engineering and Physics Sciences in Medicine Conference. Darwin, Australia.

- Harriss W.M., Bezak E., Yeoh K. (2010), *Predicting individualised responses of hypoxic head and neck cancer to radiotherapy using Monte Carlo modelling*. Oral presentation. 3rd Modelling of Tumours “MOT” Meeting. Adelaide, Australia.

- Harriss W.M., Bezak E., Yeoh K. (2010), *Algorithm development and simulation outcomes for hypoxic head and neck cancer radiotherapy using a MC model: HYP-RT*. Oral presentation. Engineering and Physics Sciences in Medicine Conference. Melbourne, Australia.

- Harriss W.M., Bezak E., Yeoh K. (2009), *Computer and tumour xenograft modelling: dynamic hypoxia in head & neck radiotherapy*. Poster presentation. RANZCR, AIR, FRO, ACPSEM Combined Scientific Meeting. Brisbane, Australia.

- Harriss W.M., Bezak E., Yeoh K., Hermans M. (2009), *Computer and tumour xenograft modelling: dynamic hypoxia in head & neck radiotherapy*. Poster presentation. Engineering and Physics Sciences in Medicine Conference. Canberra, Australia.

- Harriss W.M., Bezak E., Yeoh K. (2008), *Monte Carlo modelling of head and neck cancer oxygenation*. Oral presentation. 2nd Modelling of Tumours “MOT” Meeting. Adelaide, Australia.

- Tuckwell W.M., Marcu L., Bezak E. (2006), *Individualising radiotherapy planning through Monte Carlo modelling of radiobiological principles for head and neck carcinoma*. Oral presentation. Engineering and Physics Sciences in Medicine Conference. Noosa, Australia.

- Tuckwell W.M., van Doorn T., Marcu L. (2005), *Temporal tumour modelling for individualised radiotherapy planning of head and neck cancer*. Oral presentation. Engineering and Physics Sciences in Medicine Conference. Noosa, Australia.

Other presentations

- Harriss W.M., Bezak E., Yeoh K. (2010), *Investigating the impact of reoxygenation in radiotherapy of hypoxic head and neck cancer using MC simulation and xenograft models*. Oral presentation. Royal Adelaide Hospital, *Medical Research Staff Prize Competition*. Adelaide, Australia.
- Harriss W.M., Bezak E., Yeoh K. (2010), *Predicting the responses of hypoxic head and neck cancer to radiotherapy using MC modelling*. Oral presentation (presented by E. Bezak). ACPSEM Queensland Branch Symposium. Brisbane, Australia.
- Harriss W.M., Marcu L., Bezak E. (2006), *Monte Carlo modelling of hypoxia and radiotherapy for head and neck cancer*. Oral presentation. University of Adelaide, Medical Physics and Biomedical Engineering *Postgraduate Student Paper Competition*. Adelaide, Australia.
- Awarded first prize in the Medical Physics category
- Harriss W.M., van Doorn T., Marcu L. (2005), *Temporal tumour modelling for individualised radiotherapy planning of head and neck cancer*. Oral presentation. University of Adelaide, Medical Physics and Biomedical Engineering *Postgraduate Student Paper Competition*. Adelaide, Australia.
- Awarded equal first prize in the Medical Physics category
- Harriss W.M., van Doorn T. (2004), *Increasing the efficiency of a temporal tumour growth model*. Oral presentation. University of Adelaide, Medical Physics and Biomedical Engineering *Postgraduate Student Paper Competition*. Adelaide, Australia.

For my family