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**DETERMINING THE α/β RATIO FOR PROSTATE CANCER
USING CLINICALLY MEASURED DOSE RESPONSE DATA**

by

Marco Carlone

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in partial fulfillment of the requirements
for the degree of
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Abstract

Radiobiological parameter estimates for prostate cancer are obtained by fitting clinically measured tumour control data using both a homogeneous (individual) and heterogeneous (population) tumour control model based on Poisson statistics and the linear quadratic model of cell survival. It was found that both the homogeneous and heterogeneous models produce approximately equivalent estimates of radiobiological parameters, including the α/β ratio. However, the 95% confidence interval for the α/β ratio derived from the heterogeneous model is considerably larger than that derived from the homogeneous model.

A theory of heterogeneity for tumour control modeling has been developed to explain the findings of the model fitting. This theory shows that when modeling clinical data with a heterogeneous tumour control model, estimates for α and $\ln(k)$ form a linear relationship whose slope is also an estimate of the reciprocal dose of 50% tumour control. A formula for the α/β ratio is derived using the heterogeneous tumour control model. This formula is nearly identical to the relation obtained using the homogeneous tumour control model, but the new formula includes extra terms showing that the α/β ratio explicitly depends on survival level and heterogeneity.

The ability of the linear quadratic model to accurately describe large fraction doses is also investigated. A representation of the linear quadratic model that can be used to derive the full linear quadratic equation including the Lea Catcheside dose protraction factor has been devised. This representation clearly shows that the linear quadratic model can only be derived using a little known assumption: the diminution of sub-lethal damage due to exchange of repairable lesions is negligible compared to that due to repair. This assumption was known to Lea, but it has not been reconsidered since very early work on cell survival. Removing this assumption gives a new cell survival expression that retains the linear quadratic formalism. At low doses, this model predicts linear-quadratic behaviour, which gradually changes to mono-exponential at high doses, which is consistent with experimental observations of some cell survival.

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Contents

Abstract	iii
Acknowledgements	v
Glossary	xvii
1 INTRODUCTION	1
2 RESPONSE OF CELLS TO RADIATION	7
2.1 Theory of the linear quadratic model	11
2.1.1 Derivation of Chadwick and Leenhouts	14
2.1.2 Dose rate dependence	17
2.2 Importance of the linear quadratic model	21
2.2.1 α/β ratio	21

2.2.2	Early and late responding tissues	24
2.2.3	Explanation of fractionation in radiotherapy with the linear quadratic model	24
3	CLINICAL RADIOBIOLOGY	30
3.1	Tumour control probability	34
3.2	Normal tissue complications	37
4	OPTIMIZATION OF TCP/NTCP USING HYPOFRACTIONATION FOR PROSTATE CANCER: THE BRENNER AND HALL PAPER	39
4.1	Estimating radiobiological parameters from clinical data.....	43
4.2	Objective of the thesis.....	46
5	EFFECT OF POPULATION HETEROGENEITY IN RADIOSENSITIVITY ON ESTIMATES OF THE α/β RATIO FOR EARLY STAGE PROSTATE CANCER	47
5.1	Methods and materials	49
5.1.1	Tumour control model	49
5.1.2	Clinical data	52
5.1.3	Objective Function	55
5.2	Results	56
5.2.1	Results of tumour control modeling for the heterogeneous (population averaged) model	56
5.2.1.1	Effect of non-linearity of the model	59

5.2.2	Results of tumour control modeling for the homogeneous model	64
5.2.3	Combination of parameter estimates to obtain an estimate of the α/β ratio	67
5.3	Discussion	72
6	THEORETICAL CONSIDERATION FOR POPULATION HETEROGENEITY IN TUMOUR CONTROL MODELING	75
6.1	Parameter scaling of the heterogeneous tumour control model	76
6.2	The meaning of the slope of the α vs. $\ln(k)$ parameter estimates	81
6.2.1	A direct procedure to obtain parameters for the heterogeneous tumour control model	82
6.2.2	Slope of α vs. $\ln(k)$ parameter estimates	90
6.3	Expressions for the α/β ratio using scaled parameters	97
6.4	Heterogeneous isoeffect analysis	101
6.5	Discussion	104
6.5.1	Possible bias of parameter estimates	104
6.5.2	Link between isoeffect analysis and dose response modeling .	107
6.5.3	Confidence intervals	108
6.5.3.1	Dose escalation analysis	108
6.5.3.2	Isoeffect analysis	109
7	DISCUSSION	112

8	FUNDAMENTAL LIMITS OF THE LINEAR QUADRATIC MODEL	120
8.1	Derivation of linear quadratic and modified linear quadratic equations .	125
8.1.1	Derivation of the G factor with comparison to Dale's 1985 method	125
8.1.1.1	Constant Dose Rate	125
8.1.1.2	Decaying radioactive sources	128
8.1.2	A modified linear quadratic model that accounts for simultaneous exchange and repair of sublethal damage	130
8.1.2.1	Constant dose rate	130
8.1.2.2	Decaying dose rate	132
8.1.2.3	Survival curve	132
8.2	Comparison of the linear quadratic and the modified linear quadratic model with experimental data	134
8.3	Discussion	140
8.3.1	Link between modified linear quadratic and other models	140
8.3.2	Influence of constant final slope on α/β estimate	142
8.3.3	Influence of the quality of cell survival data	143
8.3.4	α/β for other cell survival models	144
9	CONCLUSIONS	146
10	FUTURE WORK	148

10.1	Tumour control model	149
10.2	Cell survival characteristic relating to cell cycle	151
A	ADDITIONAL CELL SURVIVAL MODELS	153
1	Target theory	153
2	Repair saturation models	155
3	Lesion interaction models	160
3.1	Derivation of linear quadratic model due to Kellerer and Rossi	160
3.2	Cybernetic model	162
3.3	The repair Misrepair model	166
3.4	Lethal and potentially lethal model	170
3.5	Two-lesion kinetic	172
B	THE LYMAN NORMAL TISSUE COMPLICATION MODEL	175
C	REDUCTION OF A DOUBLE INTEGRAL FOR TUMOUR CONTROL OVER α AND β TO A SINGLE INTEGRATION OVER A COMBINED VARIABLE $\alpha + \beta d$	179
D	A MONTE CARLO BASED TUMOUR CONTROL MODEL	183
E	CONFIDENCE INTERVALS FOR α/β AND OTHER PARAMETERS	187
	REFERENCES	190

List of Figures

2.1	Survival curve for HeLa cells.	12
2.2	The dose rate effect showing different survival characteristics for Chinese hamster cells exposed to ^{60}Co at different dose rates.	18
2.3	The isoeffect data of Withers.	27
4.1(a)	The difference in survival predicted by the linear quadratic model for doses given in a single fraction (dashed line) and for doses given in two and three Gy per fraction for a tissue with α/β ratio of 10 Gy (typical of many tumours).	41
4.1(b)	The difference in survival predicted by the linear quadratic model for doses given in a single fraction (dashed line) and for doses given in two and three Gy per fraction for a tissue with α/β ratio of 1.5 Gy.	41
5.1	Dose response data recorded by Stock, Pinover and Hanks. Numerical values are given in Tables 5.1 to 5.3.	54
5.2	Parameter estimates for Eq. (5.3) using the Monte Carlo tumour control model described in Appendix D and the clinical data of Stock, Pinover and Hanks. The confidence intervals were constructed using the constant Chi-	

Square boundary technique using $\Delta\chi^2 = 5.99$ for two free parameters ($\ln(k)$ was held fixed) and 95% confidence limit.	57
5.3(a) Parameter estimates for Eq. (5.3). using a numerical integration for the heterogeneous tumour control model, Eq. (5.2) and the clinical data of Stock, Pinover and Hanks. The confidence intervals were generated by a Monte Carlo technique that is described in Appendix E.	61
5.3(b) Estimate of the parameter σ/α derived from the data in Fig. 5.3(a) for the three published data sets used this study. The errors bars represent the 95% confidence intervals, and were generated using the Monte Carlo method of Appendix E.	62
5.3(c) The distribution of χ^2 obtained for Fig. 5.3(a) and 5.3(b).	63
5.4(a) Estimates and 95% confidence intervals of the α and α' parameters obtained when fitting to the same clinical data as Figures 5.2 and 5.3 using the homogeneous model, Eq. (3.3).	65
5.4(b) The distribution of χ^2 obtained when plotting Fig. 5.4(a).	66
5.5(a) Plots of the α/β ratio as a function of $\ln(k)$ using the homogeneous fit results given in Fig. 5.4(a).	70
5.5(b) Plots of the α/β ratio as a function of $\ln(k)$ using the heterogeneous fit results given in Fig. 5.3(a).	71
6.1(a) A three-dimensional plot of tumour control probability given by Eq. (5.2), as a function of the new variables κ , and A	78
6.1(b) Contour plot of Fig. 6.1(a) in increments of 5%, starting at 5% for the leftmost isoline. For a large part of the parameter space, ($A = \sigma D > \sim 1$), the isolines are linear whose asymptotes all intersect the point $\kappa \approx 0.577$, $A = 0$	79
6.2(a) Tumour control probability as a function of dose data used to illustrate the procedure for estimating radiobiological parameters given in Section 6.2. These points were generated with $\overline{\alpha'} = 0.16 \text{ Gy}^{-1}$, $\sigma = 0.04 \text{ Gy}^{-1}$, and $\ln(k) = 10$ using the Monte Carlo method to evaluate tumour control given in Appendix D.	83

6.2(b)	The data used to plot Fig. 6.2(a) plotted in the κ - A parameter space.	84
6.2(c)	The sets of κ - A parameter coordinates obtained using the procedure outlined in Section 3.3 and the data given in Fig. 6.2(a). The lowest set was constructed using $\sigma = 0.01 \text{ Gy}^{-1}$; the highest set was made with $\sigma = 0.15 \text{ Gy}^{-1}$. The fourth set from the bottom was constructed from the true σ , 0.04 Gy^{-1} , and this is the only set of coordinates that forms a perfect linear relationship.	87
6.2(d)	Parameter estimates obtained using the extension to the procedure given in Section 6.2 and the pseudo-clinical data given in Fig. 6.2(a). The top graph is the quantity $H = \sigma/\alpha$, which is the slope of each set of κ - A coordinates from Fig. 6.2(c) plotted against the negative x -intercept, $\ln(k)$. The middle graph is the value of σ used to construct each set of κ - A coordinates in Fig. 6.2(c) divided by the slope of the coordinates (σ/α) plotted against the negative x -intercept, $\ln(k)$. The bottom plot shows the deviation of each curve in Fig. 6.2(c) from linearity by plotting the sum of the deviations from the best-fit line squared for each set of κ - A parameters in Fig. 6.2(c).	88
6.3(a)	Comparison of parameter estimates obtained using the method of parameter scaling with the method of maximum likelihood. Top: a dose response for an LDR treatment was constructed with a dose of 50% tumour control of 40 Gy and using $\ln(k)$ equal to 20. α estimates evaluated at $\ln(k)$ 20 are plotted, with 95% confidence intervals, for dose response constructed with H (σ/α) = 0.05 to 0.3. The true value of α is plotted as a dotted line. Middle and bottom: similar parameter estimates for α as obtained for the top plot, but with the 50% dose equal to 60 Gy, and 80 Gy.	94
6.3(b)	Comparison of estimates for the inverse slope of the α vs. $\ln(k)$ plot using the method of parameter scaling and the method of maximum likelihood. Top plot: $D_{50} = 40$, middle: 60 Gy, bottom: 80 Gy. For each plot H was varied from 0.05 to 0.3. The true values are also plotted as a dotted line. ...	95
6.3(c)	Comparison of estimates for σ using the method of parameter scaling and the method of maximum likelihood. The value of σ plotted is at the value for $\ln(k) = 20$ for the three D_{50} values (plotted on x -axis), for $H = 0.05$ (top left) to 0.3 (bottom right). The true value of H is shown as a dotted line. As for Fig. 6.3(a), the method could not estimate a value for H when the true H is low, and D_{50} is large.	96

6.4	The α/β ratio plotted using Eq. (6.6) and the values for κ and D given in Table 6.2.	100
6.5	Parameter estimates and clinical data for three clinically measured dose response studies for prostate cancer. Top: Low dose rate ^{125}I therapy of prostate cancer (Stock), middle and bottom: 2 Gy per fraction external beam therapy (Pinover and Hanks). The parameter estimates plotted here are derived from the linear relation of α and $\ln(k)$ parameters that are obtained when fitting a heterogeneous (population) and homogeneous (individual) tumour control model to clinical data. The numerical values are given in Tables 6.1 and 6.2.	106
8.1	Compartmental model that is used to derive the linear quadratic formalism for cell survival including the Lea-Catcheside dose protraction factor. The symbols A, B and C are explained in Section 8.1.1.1.	124
8.2	Compartmental model that considers simultaneous repair and exchange of sub-lethal damage.	124
8.3	Cell survival fitting to several cell lines.	137
8.4	Model fitting of measured cell survival of several cell lines with the high dose points removed.	138
8.5	Model fitting of measured cell survival of several cell lines using only the low dose portion.	139
A.1	Schematic diagram of the Cybernetic model.	163
A.2	Schematic diagram of the Repair-Misrepair Model.	168
A.3	A schematic of the lethal potentially lethal model.	171
A.4	A schematic representation of the two-lesion kinetic model.	174

List of Tables

2.1	Linear analysis of the different tissues plotted in Fig. 1.3 using Eq. 1.23.	28
5.1	Clinical outcome for low dose rate, permanent seed brachytherapy implants as reported by Stock.	53
5.2	Clinical outcome for constant dose per fraction for PSA < 10 ng/ml as reported by Pinover.	53
5.3	Clinical outcome for constant dose per fraction for PSA 10 - 20 ng/ml as reported by Hanks.	53
6.1	Linear Fits of Fig. 5.5(a) to α vs. $\ln(k)$ with 95% confidence intervals for fits using the homogenous model.	101
6.2	Linear Fits of Fig. 5.5(b) to α vs. $\ln(k)$ with 95% confidence intervals for fits using the heterogeneous model.	101
6.3	Confidence intervals for individual α/β values (in Gy) as calculated using Eq. (6.17) and a Monte Carlo synthetic data method to generate the confidence intervals for individual α/β based on the population mean and variance of α and β . For all entries, $D_b = 145$ Gy, $D_e = 72$ Gy, $d = 2$ Gy, $TCP = 0.8$, $m = 1.2$, $\bar{\alpha} = 0.26$ Gy ⁻¹ , and $\sigma_{\alpha}/\bar{\alpha} = 0.3$	110

Glossary

α	Term representing the non-repairable cellular damage in the linear quadratic model that arises from a single radiation event (no interaction).
α'	Term used in this thesis to represent the combined quantity $\alpha + \beta d$.
β	Term representing the non-repairable cellular damage in the linear quadratic model that arises from interaction of repairable lesions.
ϵ	Term used in Chapter 8 to represent the probability of interaction of repairable lesions such that a non-repairable lesion is formed.
μ	The rate constant for exponential repair of sublethal (repairable) lesions.
^{125}I	Radioactive isotope used in the treatment of prostate cancer in low dose rate brachytherapy. Due to the short half-life of the isotope, the seeds do not need to be removed after they have been implanted in the prostate.
A	Term used in the derivation of the linear quadratic equation of Chapter 8. 'A' represents the number of potential sites within a

cell where a lesion can be formed.

B	Term used in the derivation of the linear quadratic equation of Chapter 8. 'B' represents the number of repairable lesions that are created per cell as a result of exposure to ionizing radiation.
Brachytherapy	A technique in radiotherapy whereby a radioactive material is implanted within the tumour.
BED	Biologically effective dose. This is the dose where equivalent cell survival would occur when cells are exposed at a low dose rate.
bNED	Biological No Evidence of Disease. In prostate cancer, this corresponds to the used of PSA in determining the presence of prostate cancer cells.
C	Term used in the derivation of the linear quadratic equation of Chapter 8. 'B' represents the number of non-repairable lesions that are created per cell as a result of exposure to ionizing radiation.
Clonogen	A cell that is capable of replicating indefinitely so that it populate a tumour.
<i>D</i>	The total dose administered in radiation therapy.
<i>d</i>	The dose per fraction used for fractionated radiation therapy.
DNA	Deoxyribonucleic acid. An organic acid consisting of four nitrogen bases (adenine, thymine, cytosine and guanine), which exist in a double helix structure. DNA is the genetic material of most organisms.
External beam therapy	Radiation therapy where the source of radiation is from outside of the patient (unlike brachytherapy). For modern radiotherapy, this source is a linear accelerator, however, it can also be a from a Cobalt 60 unit or orthovoltage unit.
$H = \sigma/\alpha$	The coefficient of variation of the α parameter of the linear quadratic model in a population of tumours where the variance of α is σ_{α}^2 .

Hyperfractionation	Administration of radiotherapy with small doses per fraction. Small is typically define as less that 2 Gy.
Hypofractionation	Administration of radiotherapy with large doses per fraction. Large is typically greater that 2 Gy.
Isoeffect	A term used in TCP and NTCP where an effect is some type of biologically based observable, such as tumour control, of normal tissue complications. Isoeffects are biological endpoints that are considered equivalent.
k	A symbol used in this thesis used to denote the number of tumour stem cells.
lesion exchange	A process by which two repairable lesions interact to form an non-repairable lesion. It is also denoted a lesion interaction.
lesion interaction	A process by which two repairable lesions interact to form an non-repairable lesion. It is also denoted a lesion exchange.
lesion repair	Repair of a double strand DNA break by either homologous, or non-homologous end joining
LET	Linear Energy Transfer. The amount of energy deposited per unit distance of an ionizing particle while being attenuated in a medium.
LQ	Linear quadratic model.
$\ln(k)$	The natural logarithm of the number of tumour clonogens or stem cells.
NTCP	Normal Tissue Complication Probability. The probability, expressed in percent, that a healthy tissue will undergo sufficient damage such that a clinically relevant complication is expressed.
p	A symbol used in Chapter 8 which represents the yield of repairable lesions per unit dose.
PSA	Prostate Specific Antigen. This is measured using a blood test. The concentration of the antigen is believed to correlate with the number of prostate cells, including the number of cancerous cells. A marked increase is an indicator of prostate tumour progression.

R	A symbol used in Chapter 8 which represents the dose rate.
RBE	Relative biological Effectiveness. The is a ratio between the dose required to achieve a certain survival for a photon beam at 250 kV with the dose the beam of interest to give the same survival.
RE	Relative Effectiveness. The ratio of doses for an exposure at low dose rate to high dose rate for equivalent survival.
Stemcell	A cell which is believed to have the ability to replicate indefinitely, thus being able to repopulate a tumour. Also called a clonogen.
TCP	Tumour control probability. The probability that a tumour has been removed given the dose administered.
Teletherapy	A synonym for external beam therapy.

Chapter 1

INTRODUCTION

The field of radiobiology has evolved from its beginnings in the early twentieth century to a stage where considerable knowledge of the response of cells to ionizing radiation as measured in laboratory conditions is now known. This characterization of cellular response to radiation has been achieved by distinguishing several fundamental phenomena, which are summarized into two general and broad groups. The first is the natural response, which is the cell's inherent ability to survive injury due to ionizing radiation; the second is the modification of this basic reaction due to environmental conditions. These modifying factors are numerous and complicated, reflecting the inherent sophistication of the cell; they are principally caused by the physical characteristics of the ionizing radiation and the cell's chemical environment. In very

broad terms, the field of radiobiology involves the detailed understanding of deleterious effects of ionizing radiation on cellular survival by classifying these in terms of a fundamental response that can be modified by many environmental circumstances.

The underlying purpose of the development of the field of radiobiology is twofold: the desire to come to a fundamental understanding of the mechanism involved in cell death due to ionizing radiation and to the application of this knowledge to other problems important for society, the protection of the public from the potential hazards of ionizing radiation, and to the medicinal uses of ionizing radiation. An important, and driving force in the development of radiobiological principles is the use of ionizing radiation in the treatment of cancer. The history of therapeutic uses of ionizing radiation in cancer therapy has closely paralleled developments in radiobiology, since it was realised at almost the same time as ionizing radiation was discovered that x-rays could be used therapeutically to treat cancer.

The practice of radiotherapy, and the technology involved in delivering radiotherapy, has evolved considerably since the first uses of ionizing radiation in the treatment of cancer, almost a century ago. In particular, there has been a rapid progression in the past twenty years as radiotherapy has become more widespread in clinical use. Currently, the technology of radiotherapy involves sophisticated, room size linear accelerators that are equipped with x-ray beam shaping, modulating and delivery tools capable of producing complicated dose distributions on a routine basis.

This ability is the result of great technological advances in: (1) radiation dosimetry, the ability to measure precisely the dose delivered by the linear accelerator; (2) dosimetry planning, where the orientation and delivery parameters of the linear accelerator are calculated using a treatment planning computer and calculation methods based on the fundamental interactions between radiation and matter; and (3) increased availability of advanced linear accelerator control systems which permit the routine set up of the linear accelerator for these purposes.

The application of radiobiology to the treatment of cancer has been more slowly incorporated in the daily operations of radiotherapy. A principal problem with the field of clinical radiobiology is that it has not been developed sufficiently so that results from the radiobiology laboratory can replace clinical judgement. Experimental measurements of radiobiological parameters that can be used clinically are extremely difficult to obtain, since tumours *in vivo* are subjected to a host of different environments which are simply too complicated or difficult to reproduce *in vitro*. Despite a good understanding of the cellular radiosensitivity of laboratory samples, the extrapolation of parameters required to calculate a quantifiable effect in clinical radiotherapy are not yet readily obtainable with sufficient precision. There is a further complication since, for many clinical diseases, it is not clear what degree individual environmental factors contribute to cell survival. Even in the simplest case involving the dose delivered to the tumour target, despite great technological advances in dose calculation and delivery, there is not yet a readily available method to measure the actual dose delivered to the

target area post treatment, in a routine and non-invasive manner.

The difficulty in applying the principles of radiobiology to the practice of radiotherapy has led to considerable literature activity in the past ten or fifteen years which was dedicated to different specific problems applicable to clinical radiobiology. There are many different goals and justifications for this line of investigation. One goal is the development of techniques designed to assist clinical decision making, such as biologically based methods to evaluate and rank treatment plan strategies or to estimate normal tissue complications associated with competing treatment plans.¹⁻³ Equally importantly, clinical radiobiology also includes the development and refinement of methods that can be used to determine radiobiological parameters directly from clinical observations, enabling an *in vivo* measurement of radiobiological parameters. The many difficulties are analogous to the problems of *in vitro* methods. In order to estimate radiobiological parameters from clinical outcome, an appropriate model of the tumour and healthy tissue, as well as the processes that relate to tumour cure or complication are required. Since the tumour's environment is complicated, and unknown, there is considerable difficulty associated with formulating and applying an appropriate model. Furthermore, even if appropriate models can be formulated, it is unclear if the necessary parameters for these models can be extracted from clinical data since realistic models may involve multiple parameters that are correlated. This may prohibit the measurement of useful radiobiological parameters directly from clinical data.

The practice of estimating radiobiological parameters using clinically measured outcome is a new field, which is still in its infancy. There is considerable debate in the radiotherapy and medical physics literature as to what the best approaches are, and what level of model complexities are required to determine radiobiological parameters that can be useful in radiotherapy practice. The purpose of this thesis is to examine a small part of this greater problem: to quantify the effect of population averages in the measurement of a specific number, which is in fact a ratio of two parameters, α and β , or the α/β ratio. The meaning of this ratio is discussed in detail throughout this thesis. The reason this problem was chosen is because it is the author's belief that the fundamental problem for parameter estimation from clinical observations of radiotherapy outcome is one of measurement. In cases where the intent of therapy is to remove the disease (curative), outcome is normally characterized as a success or as a failure. Because of this, measurements of radiotherapy outcome necessarily involve the measurement of an averaged outcome of many patients. Inter-patient variations of response to radiation play an important and fundamental role in characterizing dose response. The literature is currently ambiguous on the issue of whether consideration of inter-patient differences is required to accurately estimate radiobiological parameter ratios, and further, the theoretical methods for effectively dealing with heterogeneity are limited and under developed.

The objective of this work is to investigate the meaning and significance of α/β estimates of early stage prostate cancer that can be obtained from applying a tumour

control model to clinically measured dose response. The approach used in this thesis is to limit the study of heterogeneity to a single quantity, which is the inherent radiosensitivity of a patient. A methodology for effectively incorporating this heterogeneity in the tumour control model is developed, and methods of expanding the current findings to a more general case are presented in the discussion. The format of this work is as follows: Chapters 2, 3 and 4 introduce the field of clinical radiobiology. In Chapter 5, estimates for the α/β ratio are obtained using a heterogeneous tumour control model applied to clinical data. Chapter 6 outlines a detailed theory of tumour control modelling which specifies the limits of knowledge that can be derived using a heterogeneous (population averaged) tumour control model. Chapter 7 provides a critical discussion of the principal results of Chapter 5 and 6, and introduces the question of large dose per fraction, hypofractionation. Chapter 8 continues by discussing a little known assumption of the linear quadratic model, and develops a detailed theory of the model in the goal of examining the fundamental ability of the concept of α/β to adequately describe cell survival at large dose per fraction. Chapter 9 provides a summary of conclusions, and Chapter 10 outlines directions of future work. Several appendices are included for completeness. Appendix A provides a detailed discussion of cell survival model concepts; Appendix B introduces the concept of normal tissue complication; Appendix C shows how consideration of heterogeneity in α and β can be reduced to heterogeneity in a single combined quantity; Appendix D outlines a Monte Carlo implementation of a tumour control model; and Appendix E discusses error analysis.

Chapter 2

RESPONSE OF CELLS TO RADIATION

When exposed to ionizing radiation, living tissues undergo changes that result in a reduction of the number of viable cells. The manner used to define how the reduction is calculated depends on the type of cell and its normal function. In the case of cells that are not actively proliferating, cell death can be defined as loss of function.⁴ For cells that are actively dividing, cell death is defined as its loss of ability to divide and multiply. For cancer cells, the loss of the ability to undergo mitosis, or production of non-viable progeny, can be defined as cell death since cancer cells must retain the ability to multiply. In radiobiology, cell survival is defined as the proportion of cells that retain the ability to form a colony of daughter cells after exposure to ionizing

radiation.

The mechanism that creates a biological lesion from exposure to ionizing radiation is the creation of a fast electron in the cellular material from the interaction of an incident photon by either the photoelectric, Compton or pair production processes. The frequency of occurrence of each type of interaction depends on the energy of the incident photon and the chemical composition of the target material. In the case of cellular material, the target material is about 80% water and in the range of x-ray energies used in radiotherapy, the Compton process is dominant; the creation of a fast recoil electron ionizes the water molecule. The ionized water molecule can react with another water molecule to produce a hydroxyl radical (OH•). These reactions are⁴:

The hydroxyl radical is highly reactive and has a lifetime on the order of nanoseconds, which is sufficient for it to diffuse a short distance and react with a target molecule, causing a biological lesion. The exact nature of the target molecule is not known precisely, however, there exists considerable evidence and it is widely speculated that the most important target for consideration of cell survival is the DNA molecule.⁵ The process by which the hydroxyl radical diffuses is referred to as an indirect lesion action, and is more typical of lower LET particles such as the photons used in radiotherapy. For higher LET particles such as neutrons or α -particles, the atoms of the target may be

directly ionized, initiating the process that can create a biological lesion, using what is called a direct action.

The above processes occur in a time scale on the order of 10^{-15} seconds for the ionisation, 10^{-10} seconds for radical formation, 10^{-9} seconds for the formation of a biological lesion, and 10^{-5} seconds for the radical formed by interaction of the hydroxyl molecule and the biological material. The onset of a biologic effect, however, is considerably longer than these time scales, and can be on the order of hours, days, weeks, years or even generations, depending on the exact nature of the biological lesion.⁴ In radiobiology, and thus cell survival modelling, the type of biological lesion considered is one that will prevent the cell from replicating indefinitely; it is generally believed, and there is experimental evidence to show that a single cellular lesion can transform a viable cell into one that is doomed to die when the cell attempts to divide at mitosis.⁶ If the DNA is considered to be the principal target in the cell, this definition of biological lesion could be restated as the occurrence of a DNA double strand break of sufficient importance to form a chromosomal aberration that would prevent mitosis and cell division. In mathematical terms, the probability of formation of a biological lesion relevant to cell survival modelling could be written:

$$P_{\text{lesion}} = P_{\text{ion}} \times P_{\text{chem}} \times P_{\text{biol}}, \quad (2.1)$$

where P_{ion} is the probability of ionizing a target molecule, P_{chem} is the probability the ionization results in chemical damage to a biologically relevant target, and P_{biol} is the

probability the biological damage is of sufficient importance to cause a chromosomal aberration.

The result of this process is binary: a photon incident upon a biological material will either create or not create a biological lesion. In typical cell survival experiments, and most irradiation conditions used in radiotherapy, the number of incident photons is considerably larger than the biological lesions created. The overall probability that an incident photon will create a biological lesion is very small, but biological damage can be ensured by using a sufficiently large fluence of incident photons. If these assumptions are true, then the occurrence of P_{lesion} should follow a Poisson distribution, which is the limiting case of a binomial distribution as the probability of success tends to zero but there are sufficiently large numbers of attempts so that there are a finite number of successes.

This assumption of Poisson statistics is the essential assumption of most of the cell survival models that have been proposed in the literature (see Appendix A). In general, the method of cell survival models is to obtain an estimate for the number of lethal lesions created per cell per unit of exposure (dose), where a lethal lesion is defined as a lesion of sufficient importance so that it will generate a chromosomal aberration and cause reproductive cell death. Survival probability is determined by calculating the probability that no lethal lesions exist given the expected mean number of lesions created. Using the assumption that the lesion formation follows a Poisson

distribution, the probability that no lesions are formed is given by:

$$S = f(n; \nu) = \frac{\nu^n}{n!} e^{-\nu}. \quad (2.2)$$

We are interested in the probability the number of lesions created, n , is zero, given ν expected lesions per cell, so survival is given by:

$$S = e^{-\nu}. \quad (2.3)$$

Experimental evidence for the Poisson model is given by the correspondence of the number of chromosomal aberrations and the natural logarithm of cell survival.⁶

2.1 Theory of the linear quadratic model

Cell survival experiments on mammalian cells have repeatedly shown a distinctive form of cellular dose response. When the dose response is plotted on a semi-log scale, it is characterized by a finite, non-zero, initial slope that is followed by a shouldered portion, which gradually transforms into a final linear portion. The initial and final slopes as well as the size of the shoulder are cell type dependent, but they are present in some form for virtually all cell types, except for the very radiosensitive cells, or for cell survival experiments performed with high LET radiation. An example of a typical photon cell survival curve is given in Fig. 2.1, which is survival for HeLa cells⁷ derived from a human cancer of the cervix cell culture.

FIG. 2.1. Survival curve for HeLa cells. Adapted from Puck, T.T. and Marcus, P.I., "Action of x-rays on mammalian cells", *J.Exp.Med.*, **103**, pp. 653-666, (1956)

Three general categories of cell survival theories have been proposed and developed in the literature. These are: the target theory; the saturation models; and the lesion interaction models. Specifics of these cell survival models are given in Appendix A. The target theory was the original cell survival model and was used extensively in describing cell survival curves from the time when mammalian cell survival curves became available until it was eventually replaced by the more fashionable linear quadratic model. The target theory model suffers from a poor representation of the initial part of the survival curve. The saturation models predate the more modern lesion interaction models, and in many ways are more appealing since they offer a good description of the entire survival curve with the fewest number of parameters. They have never been widely applied either in radiobiology or radiotherapy, but have many practical as well as conceptual advantages. Lesion interaction models combine target theory with repair mechanisms, and consist of the very simple linear quadratic model, to the conceptually challenging two-lesion kinetic model. In this introduction, the linear quadratic model as originally proposed by Chadwick and Leenhouts is described, along with a development of the dose rate dependence.

2.1.1 Derivation of Chadwick and Leenhouts

The linear quadratic model was independently developed by Chadwick and Leenhouts⁵ and Kellerer and Rossi⁸ using different approaches. The approach by Chadwick and Leenhouts was to consider the critical target in the cell to be the DNA molecule, and the critical lesion to be the double strand break of the DNA molecule. They considered formation of a double strand break by two mechanisms: either a direct formation of double strand break by a single radiation event, or by the interaction of two single strand breaks that are in close physical proximity so that the net result of the two single strand breaks is one double strand break. The mathematical formulation of the model proceeds as follows:

Let n_I be the number of chemical bonds on strand 1 of the DNA double helix where a single strand break can occur and let n be the number of remaining bonds after dose D is administered. The yield of single strand breaks per unit dose is assumed to be proportional to the number of potential sites. Using k as the proportionality constant, this is written:

$$\frac{dn}{dD} = -kn, \quad (2.4)$$

$$n = n_I e^{-kD}. \quad (2.5)$$

The number of single strand breaks (ssb) on stand 1 is $n_I - n$:

$$ssb_I = n_I (1 - e^{-kD}). \quad (2.6)$$

Similarly for strand 2 and for double strand breaks (dsb):

$$ssb_2 = n_2(1 - e^{-kD}), \quad (2.7)$$

$$dsb_{direct} = n_0(1 - e^{-k_0D}), \quad (2.8)$$

where n_2 is the number of chemical bonds on strand 2, and n_0 is the total number of sites where a dsb can occur. If we consider that there is a probability ϵ that a single strand break on strand 2 is sufficiently close to a single strand break on strand 1, the number of double strand breaks that result from interaction of two single strand breaks is $\epsilon s_1 s_2$.

$$dsb_{inter} = (\epsilon)(n_1)(n_2)(1 - e^{-kD})^2. \quad (2.9)$$

The total number of double strand breaks is the sum of Eq. (2.8) and (2.9):

$$dsb = n_0(1 - e^{-k_0D}) + (\epsilon)(n_1)(n_2)(1 - e^{-kD})^2. \quad (2.10)$$

Survival probability is calculated using Eq. (2.3), where v is given by (2.10):

$$S = \exp [-n_0(1 - e^{-k_0D}) - (\epsilon)(n_1)(n_2)(1 - e^{-kD})^2] \quad (2.11)$$

The next step in the derivation is to assume that k or k_0 is small, so the products kD and k_0D are also small. The expansion of the two exponentials in an infinite series while keeping only the first term gives

$$S = \exp [-n_0 k_0 D - (\epsilon)(n_1)(n_2)(k^2) D^2]. \quad (2.12)$$

Replacing products of terms with single constants:

$$S = \exp(-\alpha D - \beta D^2) \quad (2.13)$$

This is the general form of the linear quadratic formula. The present derivation omits some steps taken in the original paper, including the consideration of repair.

Chadwick and Leenhouts treated repair as a constant proportionality factor reducing the number of single strand breaks in Eq. (2.6) and (2.7) by a fixed amount. As well, Chadwick and Leenhouts introduced a multiplier p to the square brackets of Eq. (2.12) to indicate that only a fraction of double strand breaks lead to cell death. There are several points on which the original derivation for the linear quadratic model can be criticized. The first is in Eq. (2.4) where it is not customary to suggest that the yield of lesions is proportional to the number of potential sites. It is more customary to suggest that the production of lesions is proportional to the dose (see Appendix A), and so Eq. (2.6) would normally be $n = kD$. Using this form for Eq. (2.6) removes the need to expand the exponential function in Eq. (2.11) in an infinite series and keep only the first term.

The Chadwick and Leenhouts paper considered the formation of a lethal lesion to be a double strand DNA break, which could be formed directly, or through interaction of two single strand breaks. Following the appearance of this paper in 1973, it was established that the cell has a large capacity for single strand break repair, since repair enzymes can readily use the opposite strand as a template and thus achieve high fidelity repair. (Fidelity of repair is a concept that was introduced with the Repair-Misrepair model. This is discussed in Appendix A.) It has also been recognised that double strand breaks can readily be repaired by two independent mechanisms: homologous and non-homologous repair. In homologous repair the cell uses a second DNA strand that the cell has previously synthesised as a template to rebuild a DNA

double strand break. In non-homologous repair, when a second DNA strand is not available, the cell has a mechanism at its disposal whereby it can rejoin two ends of a double strand break directly. The probability of success of a non-homologous repair is less than that of homologous repair since the cell is operating without a template. With these more recent developments in cellular repair mechanics, the original mechanism of single strand and double strand breaks discussed by Chadwick and Leenhouts has been rethought; the current understanding is that the alpha-type (linear component) damage of the linear quadratic model represents the direct formation of a chromosomal aberration from an important, complex, double strand break, since it is the number of chromosomal aberrations that correlate with cell survival.⁶ The beta-type (quadratic) damage represents the formation of chromosomal aberrations that are due to the interaction of two repairable double strand DNA breaks. The mathematics of the derivation remain the same as in the original paper (and shown here), but the meaning of the two types of lesions has been reinterpreted since this paper.

2.1.2 Dose rate dependence

One of the strengths of the linear quadratic model is the successful description of dose rate effects on cell survival curves. It has been observed experimentally that the shoulder of the cell survival curve diminishes when the exposure of the cells is performed at a reduced dose rate, as shown in Fig. 2.2. At low dose rates, the shoulder disappears completely, and the survival curve becomes an extension of the initial slope

FIG. 2.2. The dose rate effect showing different survival characteristics for Chinese hamster cells exposed to ^{60}Co at different dose rates. Data from Bedford, J.S., Mitchel, J.B., "Dose rate effects in synchronous mammalian cells in culture" *Rad.Res.* **54** pp316-327 (1973)

of the high dose rate curve. The explanation of this effect is that at low dose rate, the number of lethal lesions due to exchanges (interaction) of repairable lesions is reduced because the cell repairs these lesions before a lethal exchange occurs. The complete form of the linear quadratic model is expressed in terms of the α and β constants, as well as the repair constant for sub-lethal lesions, μ , and the time of irradiation, T:

$$S = e^{-\alpha D - G(\mu, T) \beta D^2} . \quad (2.14)$$

The function $G(\mu, T)$ is called the Lea-Catcheside dose-protraction factor, and it modifies the β term in the linear quadratic expression; its value ranges from zero at low dose rates to one at high dose rates. The Lea-Catcheside dose-protraction factor has been derived using two distinct methods, and both are originally due to Douglas Lea.⁹ Firstly, it can be derived by equating it to the ratio of the number of exchanges that occur in the presence of repair to that which would occur without repair. Lea suggested this formula to calculate this ratio⁹:

$$\int \beta n^2 dt = \beta n_0^2 \int \{f(t)\}^2 dt .$$

The parameter β is a proportionality constant such that βn^2 is the number of lesions that recombine per unit time and the function $f(t)$ is the function that describes the reduction of lesions with time. This expression was further developed by Kellerer and Rossi⁸, who formulated a general expression for the reduction of lesion exchange due to repair processes. Their expression for the ratio is:

$$G(T) = \frac{K(T)}{J(T)} , \quad (2.15)$$

where

$$K(T) = \int_0^T \tau(t) \int_0^{T-t} I(s) I(s+t) ds dt, \quad (2.16)$$

and

$$J(T) = \int_0^T \int_0^{T-t} I(s) I(s+t) ds dt. \quad (2.17)$$

The expression $K(T)$ is the entire number of lesion exchanges in the presence of some lesion reduction process (such as repair) and $J(T)$ is the summation of all exchanges possible without repair. Thus the quantity $G(T)$ is constrained to be a fraction between 0 and 1. The quantity I is the dose rate and the function $\tau(t)$ is the lesion reduction function. With constant dose rate, R , and exponential repair with repair constant μ , the $J(T)$ function evaluates to $D^2/2$, and the $G(\mu, T)$ function takes on the well-known form:

$$G(\mu, T) = \frac{2}{\mu T} \left\{ 1 - \frac{1}{\mu T} [1 - e^{-\mu T}] \right\}. \quad (2.18)$$

The ratio method can also be used to derive $G(\mu, T)$ for any dose rate, or for fractionated radiotherapy.¹⁰

The function $G(\mu, T)$ can be derived in a second way by considering rate equations for the formation and exchange of sublethal lesions. This was also originally discussed by Lea⁹ who suggested the rate equation (using his notation):

$$\frac{dn}{dt} = \xi I - \frac{n}{\tau}. \quad (2.19)$$

The variable n represents the number of sublethal lesions, ξ is a proportionality

constant relating the number of sublethal lesions to the dose rate I , and τ is the average time between lesion creation and restitution. Using this method, Eq. (2.18) has also been derived by Chadwick and Leenhouts,¹¹ and Dale.¹²

2.2 Importance of the linear quadratic model

2.2.1 α/β ratio

The material in Sections 2.2 was published in the newsletter of the Canadian Organization of Medical Physicists, InterACTIONS.¹³ The linear quadratic model is by far the most widely used model of cell survival. This success is due to the differentiation of the two most important processes that lead to cell death: death by non-repairable lesions, and death by repairable lesions. The essence of the linear quadratic model is that to a good approximation, these two processes can be described using two fixed proportionality constants, which are the well-known α and β parameters. The amount of non-repairable damage, αD , is proportional to the number of lesions formed, which in turn is proportional to the dose. The maximum number of repairable lesion exchanges, βD^2 , is proportional to the dose squared. However, these lesions are repairable by definition, so if the dose rate is low, such that there is enough time for these minor lesions, or sub-lethal lesions, to repair themselves before another lesion is formed, the amount of cell killing that is due to the repairable lesions is reduced. The linear quadratic model says that, to a first order approximation, the number of lethal lesions that will be induced in the cell as a function of dose will be

$$\alpha D + G(\mu, T)\beta D^2.$$

The linear quadratic model uses only two concepts, or mechanisms of cell death: lesions that directly lead to cell death regardless of repair, and exchange of repairable lesions that also leads to cell death. Critics of the linear quadratic model contend that this is too simple a view of a considerably complicated process. In physics, however, good theories are ones that minimize the complexity of the approach while maximizing the predictive ability of the method (the Principle of Parsimony). The most important concept of the linear quadratic model is that of the relative importance of the two processes that lead to cell death. Ignoring the dose rate effects, the relative number of lethal lesions to lethal exchanges is $\alpha/\beta D$, if we multiply this dimensionless quantity by the dose administered the resulting quantity, the α/β ratio, represents the dose where the two processes that lead to cell death have equal importance.

Tissues that have a high α/β ratio are tissues where the exchange of repairable lesions plays a low role in cell death; most cell death is due to the non-repairable, α -type lesions. For tissues with a low α/β ratio, repair plays a more important role at lower dose, and so the dose per fraction is important since larger fraction doses increase the number of lethal exchanges quadratically. Mathematically, this can be seen if we re-write the survival equation in a more useful form. For dose rate exposures typical in

radiotherapy, the dose rate factor, $G(\mu, T)$, is equal to one, and so the linear quadratic survival equation is given by Eq. (2.14).

$$S = e^{-\alpha D - \beta D^2}.$$

For fractionated exposure to cells, where a total dose, D , is given in n fractions with the dose per fraction equal to d , the survival is:

$$S = \exp\left(-\alpha D \left[1 + \frac{d}{\alpha/\beta}\right]\right). \quad (2.20)$$

In this form, it is clear how the dose per fraction and the α/β ratio relate with one another. When the α/β ratio is large as compared to d , the term in the square brackets of Eq. (2.20) will be close to one, and the survival will depend much more strongly on the total dose than on the dose per fraction. However, if the dose per fraction is of the same order as the α/β ratio, then the survival will depend not only on the total dose D , but also on the fraction size, d .

The linear quadratic model, using only two key concepts, that of repairable and unrepairable lesion formation, can be used to predict how different tissues should respond to different fractionation schemes. This approach of the model is in itself interesting. The real strength of the linear quadratic model, however, stems from a biological effect that is still poorly understood: the α/β ratio seems to be related to the time required for cells to divide and cycle.¹⁴

2.2.2 Early and late responding tissues

Tissues that have a short cell cycle are those that replicate quickly; for instance skin, mucosa, and most tumours typically have an α/β ratio of approximately 10 Gy. Tissues that have a long cell cycle are tissues that are not readily dividing; for instance brain tissue, spinal cord, lung, and kidney typically have an α/β ratio of about 3 Gy. These are often described in radiobiology by the common phrases: “early responding tissues” and “late responding tissues”. This terminology reflects that there is a cell cycle time dependence of the interval between irradiation and observable cellular response, such as the ability to form colonies in a petri dish, or by some clinically observable change, such as reddening or moist desquamation of the skin, reduced lung capacity, or paralysis. Cells that cycle quickly show the damage “early”, while cells that are slowly cycling show their effect “late”, as the effect manifests itself when the cell attempts to divide. Tissues that cycle quickly tend to have a high α/β ratio; in radiotherapy the most important tissue of this type is the tumour. Tissues that cycle slowly are typically the tissues that we want to protect in radiotherapy: the spinal cord, the lungs, kidneys, and these all tend to have a low α/β ratio.

2.2.3 Explanation of fractionation in radiotherapy with the linear quadratic model

Compelling evidence that the linear quadratic approach has merit is demonstrated by what is called iso-effect analysis. Iso-effects are different treatment

delivery strategies (dose per fraction and total dose) that give equivalent effects, either tumour control or normal tissue complication rates. It is assumed that these are due to equivalent surviving fractions. The exponent in Eq. (2.20) is often referred to as the Effect, E . We write this as

$$E = \alpha D \left[1 + \frac{d}{\alpha / \beta} \right]. \quad (2.21)$$

If we divide this equation by α , the resulting quantity, E/α is called the Biologically Effective Dose, or BED. The physical interpretation is that this is the dose that would give an equivalent surviving fraction if the exposure were given in a single fraction at low dose rate so that there would be no exchange of sub-lethal lesions.

$$BED = D \left[1 + \frac{d}{\alpha / \beta} \right]. \quad (2.22)$$

The BED is an important quantity in radiotherapy since it permits the comparison of different dose delivery protocols by creating a dose rate independent measure of survival. The effect of exchange renders the direct comparison of fractionation schemes difficult since it is affected by both the total dose and the dose per fraction. The BED addresses this by creating a quantity that is independent of exchange; the greater this quantity, the greater the deleterious effect of the exposure. Are 36 Gy at 2 Gy/fraction more effective at cell killing than 30 Gy delivered in 3 Gy fractions? If the α/β ratio is 3 Gy then the linear quadratic model says that the two protocols are equivalent, since each has a BED of 60 Gy. However, if the α/β ratio is 10 Gy, then

the 2 Gy fractions are more effective at cell killing since this BED is 43.2 Gy instead of 39 Gy for the 3 Gy fractions.

Eq. (2.22) suggests a method that can be used to obtain the important radiobiological parameter, the α/β ratio, from iso-effect analysis, where equivalent radiobiological effects are observed clinically using different treatment protocols. Rearranging Eq. (2.22) to obtain a relationship between the total dose, D , and the dose per fraction, d gives:

$$\frac{1}{D} = \frac{1}{BED} + \frac{d}{(\alpha/\beta) BED}. \quad (2.23)$$

Eq. (2.23) says that for equivalent biological effects obtained by varying the total dose and fraction dose, a plot of the inverse dose vs. the dose per fraction should yield a straight line with intercept equal to $1/BED$ and slope equal to $1/BED$ divided by the α/β ratio. Data of this type was compiled by Withers, and is shown in Figure 1 of his 1985 paper¹⁵. This graph is highly important in radiobiology, since it shows essentially linear relationships between the total dose and the dose per fraction, with late responding normal tissues having a greater slope than tumours and other early responding tissues. Figure 1 of Withers has been adapted and plotted here as Fig. 2.3 which shows a plot of the inverse dose vs. dose per fraction for several different tissues.

The linear relations between these quantities are evident. The α/β ratio of these tissues was determined by linear analysis; the results are shown in Table 2.1, which

FIG. 2.3. The isoeffect data of Withers. (Cancer, Vol. 55, pp. 2086 – 2095, 1985) Late responding normal tissues are in solid lines, and early responding tissues are in dashed lines.

Table 2.1. Linear analysis of the different tissues plotted in Fig. 2.3 using Eq. (2.23).

Tissue	α/β	Type
Kidney	0.04	Late
Lung	4.1	Late
Spinal Cord	2.4	Late
Skin Late	1.0	Late
Testis	9.5	Early
Colon	7.7	Early
Jejunum	13.4	Early
Skin Acute	8.8	Early
Fibrosarcoma	9.3	tumour

shows the general trend that early responding tissues tend to have a large α/β ratio, on the order of 10 Gy, while late responding tissues tend to have a lower α/β ratio, on the order of 3 Gy.

Fractionation in radiotherapy was formerly a difficult issue for radiation oncologists. It was recognised early in radiotherapy that altering the dose per fraction and the total dose affected the quality of the treatment, but it was not until the linear quadratic model was applied to the problem that a satisfactory and consistent understanding became available. This is convincing (although not irrefutable) evidence that the linear quadratic model focuses on the important radiobiological quantity: the relative importance of the repairable and non-repairable processes that lead to cell death. Other cell survival models (Appendix A), such as saturation repair models lack

a description of an apparently important mechanism of cell death, which is the formation of non-repairable lesions. Alternatively, lesion interaction models employ an overly complicated view of lesion interaction, rendering it difficult to describe a dose where these two mechanisms leading to cell death are equivalent. This dose could broadly be referred to as an α/β ratio. The underlying biological reasons why a correlation exists between the cell cycle and the dose where there is equal production of repairable and non-repairable lesions remains unknown. It is possible that the linear quadratic view of this problem is overly simplistic; however enough understanding of clinical radiotherapy has resulted from the linear quadratic model to warrant its almost unopposed use in radiotherapy and in radiation biology.

Chapter 3

CLINICAL RADIOBIOLOGY

The principal advocates of the linear quadratic method are Fowler,¹⁶ Withers,¹⁵ and others¹⁷ who published independent and authoritative evidence that the linear quadratic model offers credible explanations of fractionation effects observed in radiotherapy. The acceptance of this new formalism regarding cell survival, and the simplicity of the approach has led many investigators to pursue further clinical applications of the linear quadratic model. The goal of this field of investigation is to support radiation oncologists by developing methods to quantify the outcome of competing techniques in

radiotherapy. One of the principle and long standing problems in radiotherapy is how to distribute the dose to a tumour in time (dose rate) so that the treatment has a maximum chance at both success and limiting unwanted complications that may arise as a result of the treatment. Because the tumour is growing, there is an obvious need to deliver a treatment at a dose rate that is high enough to limit the tumour growth and reduce the number of tumour cells. In some cases this rate of growth is quick, with tumour doubling times in the order of days. However, if the dose rate is too high, and because most tissues that are to be protected in radiotherapy, respond to radiation in such manner that the effect typically has a strong dose squared component (low α/β ratio), there is a certain threshold where too fast a dose delivery rate will induce unwanted side effects to the treatment. It is the side effects that ultimately control the entire radiotherapy prescription since the prescription technique can crudely be described as administering as high a dose that the normal tissue can tolerate. In the case where the treatment time is reduced by applying the therapy in large dose per daily fraction, complications can be limited by reducing the corresponding total dose. In other words, the dose per fraction and total dose are not independent of each other; altering one implies adjusting the other.

A successful, but conservative approach to fractionation in radiotherapy has emerged: use a consistent dose per fraction for most cancers that is sufficiently small to limit complications, but sufficiently large so that the radiotherapy is delivered in a reasonably small time period to limit tumour growth. From many years of clinical

practice, the value of 2 Gy per daily fraction has been chosen as an optimum and general choice for almost all curable diseases. This value has been derived purely from clinical experience; it has never been suggested from any type of radiobiological experiment or calculation. Some exceptions to this rule are therapies with non-curable intent, where the intent of the treatment is palliation instead of cure, and in brachytherapy, where the dose is delivered from radioactive sources implanted within the tumour. In the latter case, the tumour itself shields the healthy tissue that we wish to spare; this approach to the treatment has a natural advantage. Dose time delivery protocols for brachytherapy have evolved quite independently from that of conventional radiotherapy, where the dose is delivered from an external source (usually a linear accelerator). Even though the use of 2 Gy fraction doses was derived clinically, it is consistent with the general observation that the α/β ratio for most normal tissues is in the 3 Gy range. By using a dose per fraction that is less than the dose where the linear and quadratic components of cell killing are equal, the quadratic dose effect of cell killing is reduced as compared to the linear dose effect, and the goal of minimizing complications is aided.

A future direction of radiotherapy is the tailoring of dose per fraction for individual diseases. Not all tumours and normal tissue have equivalent biological dose response and so it is reasonable to assume that at some time in the future, clinical radiobiology will have evolved to the point where optimum strategies have been developed for individual diseases. However, this goal is a long-term effort that will

require consensus among radiotherapy practitioners. More immediate needs are to develop tools that can help radiation oncologists discriminate between radiotherapy plans on a patient-to-patient basis. Since each patient has a unique anatomy and cancer progression, distinct treatment plans based on the patient's physical form and on the relationship of the tumour to the normal tissue (determined from imaging) are devised. By judicious choice of the treatment beam arrangement, a plan can be devised where the tumour receives significantly higher average dose than the normal tissue. It is impossible, however, to remove completely the dose to the normal tissue since normal tissue must be irradiated using beams originating from outside the patient. Normally, competing dose distribution plans are discriminated based on the clinical judgement and experience of the radiation oncologist. One of the goals of clinical radiobiology is to develop tools that would transform a physical dose distribution to a biological effect distribution, and eventually to an estimate of the probability of success of the treatment. Patient treatment would benefit from this type of information since it would reduce any clinical bias of the radiotherapist and indicate direction in those clinical cases where there is not an obvious treatment course.

In clinical radiobiology, methodologies have been developed for the consideration of both the tumour and normal tissue. These are the development of methods to quantify the control of the disease, called the tumour control probability (TCP) and methods to calculate the expected normal tissue complication probability (NTCP). Both methods depend fundamentally on the reduction of cells due to the dose, and on

some further model of the greater entity, either the tumour or the healthy organ.

3.1 Tumour control probability

To quantify the success of radiation therapy, probability of tumour control is determined from the probability that no tumour stem cells remain at the completion of the radiotherapy. To calculate this, one needs to know the initial number of tumour stem cells, the surviving fraction of stem cells after irradiation, and the probability that there are no stem cells remaining given the expected number of surviving stem cells. Distinction between tumour cell and stem cell is made; the stem cell is a seed cell that is considered able to repopulate a tumour.¹⁸ The reduction in the number of tumour stem cells is obtained using the linear quadratic model. The most usual method of calculating the tumour control probability is by applying the Poisson model.¹⁹ This model assumes that the number of remaining tumour stem cells after irradiation follows a Poisson distribution. The derivation is similar to that of Eq. (2.3). If we assume a binary distribution of surviving tumour stem cells, i.e. that tumour stem cells either survive the exposure, or do not survive, and if we further assume that the number of tumour stem cells is large and the surviving fraction is small, then the binary distribution of surviving tumour stem cells reduces to the Poisson distribution.

Using the linear quadratic parameters α and β , and assuming total dose D delivered in n discrete fractions of dose d , such that $D = nd$, the surviving fraction is:

$$S = \left(e^{-\alpha d - \beta d^2} \right)^n = e^{-\alpha n d - \beta n d^2} = e^{-\alpha D - \beta d D} = e^{-(\alpha + \beta d) D}. \quad (3.1)$$

In this study, either external beam radiotherapy or low dose rate brachytherapy is considered. For external beam therapy the dose rate is high and dose per fraction d is constant. Normally the dose rate is large enough so that the G factor, Eq. (2.18) is one. In brachytherapy, the dose rate is low and we consider the G factor to be zero, which indicates no β dependence on cell death. In both cases the quantity $(\alpha + \beta d)$, which represents radiosensitivity, is constant. For simplicity, this quantity is referred to as α' in the remainder of this work. Using the symbol k for the initial number of tumour stem cells, and k_s for the surviving number of tumour clonogens,

$$k_s = (k) (S). \quad (3.2)$$

The tumour control probability is:

$$P = e^{-k_s} = \exp(-k \exp(-\alpha' D)). \quad (3.3)$$

The above derivation is the basic tumour control model for simplified conditions. In order to transform the surviving number of tumour stem cells into a tumour control probability using Eq. (3.3), a population distribution was assumed and applied. In other words, the tumour control probability is derived from the expected fraction of tumours that contain zero stem cells after irradiation many tumours. Eq. (3.3) was derived assuming a homogenous population, and so the simplest form of the tumour control model is also known as the homogenous model. In general, fine-tuning of the tumour control model is achieved by adding extra description of the population to which the tumour control model applies. The homogeneous tumour control model is

rendered more realistic by incorporating heterogeneity in the two primary parameters of the model, α' , the radiosensitivity parameter of the model, and k , the tumour size parameter. It is often assumed that in a population of tumours (patients), the radiosensitivity parameter follows a Gaussian distribution, and the number of tumour stem cells follows a lognormal distribution.²⁰⁻²⁴ Further structure to the tumour control model is achieved by adding intra-tumour variation of parameters to the model since in Eq. (3.3) it is assumed that the dose and radiosensitivity of clonogens within the tumour is homogeneous. It is well known that, especially for brachytherapy, the dose delivered to a tumour may not be homogenous, and further, due to the non-homogenous nature of tumour construction and vasculature, it is normally expected that the radiosensitivity of individual cells within the tumour is not homogenous.^{22,25,26}

Consensus on a realistic approach to tumour control modelling has been difficult to obtain, as virtually every aspect of Eq. (3.3) can be criticized. The principal assumption of the tumour control model, that control is only achieved if all tumour stem cells are removed, has never been shown experimentally. Even if this assumption is accepted, the Poisson assumption is not universally recognized²⁷ and alternative approaches have been proposed.^{28,29} Even in the case where Eq. (3.3) is accepted, transforming it into a heterogeneous description of tumour control is also problematic, as not all authors view the Gaussian description of radiosensitivity to be valid and measurements of distributions of radiosensitivity are rare.³⁰ It is evident that there is variation in the dose distribution that is delivered to the tumour. It is also well accepted

that there is variation of the cellular radiosensitivity within the tumour that is due to the heterogeneous makeup of the tumour and its complicated vasculature. Niemierko has suggested a method for reducing a heterogeneous dose distribution to a uniform one.³ Constructing a radiosensitivity distribution has never been realistically attempted, although a procedure for this has also been suggested by Niemierko.²²

3.2 Normal tissue complications

Although the focus of this study is in tumour control modelling, some brief explanation of normal tissue complication modelling is required to define the scope of this investigation. Due to the geometrical relationship between the tumour and the remainder of the patient's anatomy, some normal tissue must be exposed to ionizing radiation as a result of radiation therapy of the tumour. As in tumour control probability modelling, several investigators have proposed and developed methods and tools for evaluating and quantifying the effects of the ionizing radiation on normal tissue. Depending on the dose and proportion of volume to which the normal tissue is exposed, there exists an associated risk of reducing the normal function of the healthy organ as more organ cells are sterilised. This is either due to irradiating an increased volume of the healthy organ, or increasing the dose to which the partial volume is exposed. Assuming that the probability of complications increases with the number of cells that are sterilised, it is generally accepted that normal tissue complication probability increases with increasing volume of the normal tissue irradiated and with increasing dose. Two general methods have been outlined in the literature to transform

an organ dose volume distribution to probability of organ complication. The first is due to Lyman; it employs a phenomenological model used to interpolate clinical results. The second method uses biological principles based on a model of the organ function and the reduction of viable cells within the organ. Specific details of both approaches are included for completeness in Appendix B.

Chapter 4

OPTIMIZATION OF TCP/NTCP USING HYPOFRACTIONATION FOR PROSTATE CANCER: THE BRENNER AND HALL PAPER

In 1999, an influential paper by Brenner¹⁴ appeared in the International Journal of Radiation*Oncology*Biology*Physics. In this paper, Brenner presented two important ideas about the relationship between radiobiology and the practice of radiotherapy. If these ideas survive the test of time, they indicate the beginnings of an important change of direction in radiotherapy from the strict use of clinical experience in guiding decision-making in radiotherapy to a real attempt at using radiobiological principles when choosing directions for the practice of radiotherapy. Using the general

observation that prostate cancer is a slowly proliferating tissue,^{*} and the relationship between cell cycle kinetics and the α/β ratio, Brenner argued that prostate cancer should have a lower α/β ratio than the value of 10 Gy typical of most tumours. The literature of cell survival experiments for prostate cancer cannot be applied to this problem since different laboratories have reported results ranging from 1 to 22 Gy.^{26,31-}

³³ In his paper, Brenner made the bold suggestion that the α/β ratio could be estimated using Eq. (3.3) together with tumour control data based on clinically observed results. In order to accomplish this, outcome from two different dose rate (fraction size) protocols are needed to resolve the quantity $\alpha + \beta d$ of Eq. (3.1) and (3.3). Brenner used the dose response for low dose rate therapy observed by Stock,³⁴ and for high dose rate therapy observed by Hanks³⁵ and Pinover,³⁶ and Eq. (3.3) to produce an estimate for the α/β ratio of 1.5 Gy [0.8, 2.2].

Such a low value for the α/β ratio for a cancerous disease that is treatable in radiotherapy has broad implications. To understand this, consider Fig. 4.1. This figure illustrates the differentiated response between a normal tissue with low α/β ratio of 1.5 Gy and a tumour with higher α/β ratio of 10 Gy. For the high α/β tissue tumour, Fig. 4.1(a), the quadratic component of cell killing is much smaller than the linear

^{*} Estimates for the doubling time of prostate cancer cells are greater than 34 days,¹⁰⁸ with a low labelling index,¹⁰⁹ the number of cells undergoing DNA synthesis, and hence replication.

FIG. 4.1(a). The difference in survival predicted by the linear quadratic model for doses given in a single fraction (dashed line) and for doses given in two and three Gy per fraction for a tissue with α/β ratio of 10 Gy (typical of many tumours).

FIG. 4.1(b). The difference in survival predicted by the linear quadratic model for doses given in a single fraction (dashed line) and for doses given in two and three Gy per fraction for a tissue with α/β ratio of 1.5 Gy.

component; there is little difference in survival after multiple fractions of either two or three Gy. Fig. 4.1(b) shows similar survival curve for a tissue with α/β ratio of 1.5 Gy. In this case, the differential response between 3 Gy fraction doses and 2 Gy doses is considerably higher than that for the tissue with α/β of 10 Gy. In the usual situation where the normal tissue has a low α/β ratio and the tumour has higher α/β ratio, there is an extra therapeutic advantage from going from large fraction doses to smaller fraction doses since the change in fraction size has little detrimental effect on the tumour, but has greater beneficial effect on the healthy tissue. Thus, hyperfractionation, the use of many small fractions to treat tumours in radiotherapy, yields a natural therapeutic benefit since an appropriate amount of cell killing to control the tumour can be administered with the minimum biological impact on the healthy tissue. However, if the typical situation of a high α/β tumour and low α/β organ at risk is not the case, then the argument for small fraction doses is not applicable. In this case, as the following example shows, larger fraction doses than the typical value of 2 Gy may be beneficial to the treatment.

The biological effect of altered fractionation for a tumour-organ system with α/β of 1.5 and 3 Gy (as opposed to the 10 and 3 Gy typical values) is demonstrated using Eq. (2.22). For early stage prostate cancer that is treatable using radiotherapy, dose escalation to 76 Gy in 2 Gy fractions gives good clinical results. If the tumour α/β ratio is 1.5 Gy, the BED is 177 Gy. Consider two points in a normal tissue that has α/β of 3 Gy: one receives full dose, the second half the dose. The BED to the healthy tissue

at the full dose point is 127 Gy, to the half dose point it is 51 Gy. If the dose per fraction is changed to 3 Gy from 2 Gy, only 20 fractions, 60 Gy total dose, are needed to obtain the same BED (177 Gy) to the tumour, instead of 38 fractions. With exactly the same normalized dose distribution the full dose point in the normal tissue receives a BED of 120 Gy and the half dose point receives a BED of 45 Gy. Both dose points receive less biologically effective dose than using the 2 Gy fraction protocol. The key point in this example is that when the differentiated dose response is less because tumour and normal tissue have similar fractionation responses, it is possible to achieve the same biological effect on the tumour that clinical experience says is sufficient to control the disease using less physical dose as long as each fraction carries more cell killing by having a larger fraction dose. If the tumour responds similarly as the normal tissue, then considerably less total dose is needed since increasing the fraction dose increases the biological effect as the dose squared. Because the total dose is significantly reduced, there can be (depending on the α/β ratio of the normal tissue) a reduced effect on the healthy tissue. The example that was given showed that this reduction might only be marginal, which would indicate a roughly equal treatment. The important point however, is that the same tumour control and similar complications were achieved using 20 fractions instead of 38, which is almost 50% more efficient in radiotherapy resource utilisation.³⁷

4.1 Estimating radiobiological parameters from clinical data

The paper by Brenner initiated considerable literature activity. The approach

was criticized by King,³⁸ who argued that Eq. (3.3) is too simple, and proposed that the appropriate tumour control model should include intra-tumour variation of radiosensitivity possibly due to the oxygen effect, or some other reason. Brenner's result was reconfirmed by Fowler,³⁹ who used the same approach as Brenner did, but with a more complete dataset, which he compiled from several centres. Both Fowler and Brenner used low dose rate clinical data from brachytherapy treatments using radioactive ¹²⁵I sources. These sources emit predominantly at low energy, approximately 28 keV, where the photoelectric interaction process dominates and there is a large proportion of Auger electrons emitted due to interaction with the low Z tissue target. The large numbers of Auger electrons increase the relative biological effectiveness (RBE) of the irradiation.^{40,41} This presents difficulty in comparing results with external beam radiotherapy, which is performed using beams of megavoltage photons that have RBE approximately equal to one. To resolve this problem, Brenner published further results using dose escalation of high dose rate brachytherapy performed using ¹⁹²Ir, which has mean energy of approximately 370 keV, where the Compton interaction process dominates.⁴² This second estimate from Brenner agreed well with his initial estimate. A number of letters⁴³ were also published indicating other clinical and radiobiological evidence for a low prostate cancer α/β .⁴⁴ Finally, King published a very simple calculation based on the large difference between total doses for external beam therapy and low dose rate brachytherapy that showed that the large increase in low dose rate brachytherapy dose as compared to external beam dose was consistent with a low α/β for prostate. Anticipating the need for guidance in

altered fractionation schemes based on hypofractionation for prostate cancer, Fowler published an editorial⁴⁵ and a full study⁴⁶ developing possible new fractionation strategies for radiotherapy of early stage prostate cancer.

Few critics of low α/β for prostate cancer emerged. D'Souza, in an editorial, observed that the large difference in doses between low dose rate brachytherapy and external beam therapy might be explainable by the non-uniform dose distribution of brachytherapy.⁴⁷ Lindsay²⁵ used similar arguments and more detailed calculations to show a comparable result. Because prostate cancer is slowly growing, all of the preceding analyses ignored tumour growth in the calculation of tumour control. Wang⁴⁸ added this effect into Eq. (3.3) and obtained a higher, but still fairly low value of 3.1 Gy for prostate α/β . Nahum incorporated measurements of hypoxia for prostate cancer in estimating α/β , and found that this could also explain Brenner's result.²⁶ Finally, I investigated the effects of the variation of inter-patient variation of radiosensitivity.⁴⁹ The result I found is that the population averaging of Eq. (3.3) allows many optimal parameter estimates that have statistically equivalent fits to the clinical data. While these parameter correlations did not significantly affect the estimate of α/β , I found that there was an important increase in the confidence interval of the estimates,⁴⁹ which considerably reduces the statistical significance of the modelling result.

4.2 Objective of the thesis

The objective of this work is to investigate the meaning and significance of α/β estimates of early stage prostate cancer that can be obtained from applying a tumour control model to clinically measured dose response. The thesis is divided into three major portions: (1) modelling results of low dose per fraction therapy using a heterogeneous model, Chapter 5, (2) theoretical explanation for the observations seen in Chapter 5, (3) a discussion of the ability of the linear quadratic model to properly describe large dose per fraction, Chapter 8.

Chapter 5

EFFECT OF POPULATION HETEROGENEITY IN RADIOSENSITIVITY ON ESTIMATES OF THE α/β RATIO FOR EARLY STAGE PROSTATE CANCER

This chapter is an extract of my first publication.⁴⁹ For prostate cancer, Brenner¹⁴ and others^{39,48} have applied a simple tumour control model, Eq. (3.3) to estimate radiobiological parameters. When Eq. (3.3) is expanded to include the population distribution of radiosensitivity, it has been shown several times for diseases other than prostate cancer that the modeling does not yield unique parameter estimates. Parameter estimates for a heterogeneous tumour control model have been observed to be highly inter-correlated.^{20,50,51} Statistically equivalent fits to clinical dose response data can be constructed using a family of α values (from the linear quadratic model), $\ln(k)$, the

logarithm of the number of tumour stem cells, and σ , the amount of heterogeneity of radiosensitivity in a patient population. These families, consisting of linear relations between α and $\ln(k)$, and α and σ , produce indeterminate parameter estimates, which have effectively prohibited tumour control modeling from being more useful in radiotherapy clinics.

The purpose of this chapter is to investigate the parameter correlation that has been observed in tumour control modeling and to use the linear relation of parameter estimates to determine the α/β ratio for prostate cancer by combining parameter estimates from multiple dose response studies done at different fractionation. I investigated the effect of heterogeneity by comparing results of both the homogenous and heterogeneous models. The heterogeneous model was calculated using a Monte Carlo implementation; it allows for the individual patient radiosensitivity to be selected from an expected Gaussian distribution of radiosensitivity in the patient population. The Monte Carlo method is used to establish the validity of the method, which can be generalized to much more complicated models. It was verified by comparing it to the calculations from numerical integration.

The α/β ratio is estimated for prostate cancer by obtaining estimates for α and β by analyzing clinical outcome data for brachytherapy and external beam therapy of the same pre-treatment clinical stage so that it can be assumed that the number of tumour clonogens is also equal. The clinical stage is primarily determined by measurement of

Prostate Specific Antigen, PSA, which is believed to correlate with the number of tumour clonogens.⁵² Since the number of tumour clonogens is not known, this method results in a plot of the α/β ratio as a function of the logarithm of the number of clonogen cells. Also presented is a comprehensive error analysis based on uncertainty in clinical outcome, which is assumed to follow a binomial distribution. Since the clinical data is made up of a small number of dose response points (which in turn represent the average outcome for a relatively small number of patient trials) the uncertainty on parameter estimates is quite large, and this large uncertainty translates to large uncertainties in the final α/β estimate. The same method of error analysis was applied to the homogeneous model. The result that I found was that the same parameter correlation is observed; however the uncertainty on parameter estimates is much less, and this translates to much smaller uncertainties in the α/β ratio than those derived from the heterogeneous model. This implies that the homogeneous model may overstate the statistical significance of the result. The heterogeneous and the homogenous model produce approximately equivalent estimates of the α/β ratio as a function of the number of clonogens. The estimates do show some dependence on the number of clonogens; however the variation in α/β is not statistically significant.

5.1 Methods and materials

5.1.1 Tumour control model

The tumour control probability for an individual was given by Eq. (3.3):

$$P = e^{-k_s} = \exp(-k \exp(-\alpha' D)) \quad (3.3)$$

where α' is $(\alpha + \beta d)$, k is the number of tumour stem cells, d is the dose per fraction and D is the total dose in the case of external beam radiotherapy. A heterogeneous tumour control model, or population model, allows for variation of the various radiobiological parameters within the population of patients, and even for variation of the parameters within the tumour. It is normal to consider a population variation of (1) cellular radiosensitivity, which is characterized by the α and β parameters of the linear quadratic model, (2) the number of tumour clonogens, and (3) the repopulation rate of tumour clonogens for quickly proliferating tumours. Further, a complete tumour control model should also reflect variation of parameters within the tumour, specifically the dose distribution (especially for brachytherapy) and variation in radiosensitivity due to zones of hypoxia. However, it is well recognized that characterization of intra-tumour parameter variation is difficult, as discussed by Niemierko, who recommended ignoring this term in a tumour control model.²² A recent analysis by Nahum has incorporated hypoxia measurements in a tumour control model that accounted for inter-patient variance in radiosensitivity.²⁶ Roberts discussed a general tumour control model that considered inter patient variation in radiosensitivity, clonogen number, and repopulation.²³ He showed that if the clonogen number is on the order of 10^5 or less, variation in radiosensitivity dominates the tumour control model. For prostate cancer, tumour growth plays a minor role in the tumour control model.¹⁴ Ignoring intra-tumour heterogeneity, and assuming the clonogen repopulation and heterogeneity in the number of clonogens is a lower order effect, a population tumour control model can be

given by considering variation in radiosensitivity, which are the α and β parameters of the linear quadratic model. For a population of tumours, with mean values of radiosensitivity given by $\bar{\alpha}$ and $\bar{\beta}$, (the bar is included to emphasize that these are the mean values of the population distribution of α and β) with variances given by σ_α^2 and σ_β^2 , assuming independent Gaussian distributions of these parameters³⁰ and with a uniform number of tumour clonogens, k , and known total dose D , and dose per fraction d , the heterogeneous tumour control probability (TCP) is given by a five-parameter model:

$$TCP = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \frac{\exp\left(-\frac{1}{2} \left[\frac{(a-\bar{\alpha})^2}{\sigma_\alpha^2} + \frac{(b-\bar{\beta})^2}{\sigma_\beta^2} \right] - k e^{-(a+bd)D}\right)}{2\pi \sigma_a \sigma_b} da db. \quad (5.1)$$

Eq. (5.1) is awkward to manipulate since it is a double integral with five parameters. It can easily be reduced to a three-parameter single integral in the important case where the dose per fraction is constant, in which case the quantity $\bar{\alpha}'$, given by $(\bar{\alpha} + \bar{\beta}d)$, is also constant. Since it was assumed that α and β are both distributed as a Gaussian, and are not correlated, the quantity $(\alpha + \beta d)$ is also distributed as a Gaussian, with mean value equal to $(\bar{\alpha} + \bar{\beta}d)$. If the variance of α is σ_α^2 , and the variance of β is σ_β^2 , then the variance of the combined quantity $(\alpha + \beta d)$ is $(\sigma_\alpha^2 + d^2 \sigma_\beta^2)$. In this special case, where α and β are independent and Gaussian distributed, and the dose per fraction, d , is constant, Eq. (5.1) can be reduced to a one-dimensional integral where the integration is over all values of variable α' :

$$\text{TCP} = \frac{1}{\sqrt{2\pi}\sigma} \int_{-\infty}^{\infty} \exp(-ke^{-x}D) \exp\left(-\frac{(x - \bar{\alpha}')^2}{2\sigma^2}\right) dx \quad (5.2)$$

σ^2 is $(\sigma_{\alpha}^2 + d^2 \sigma_{\beta}^2)$, and the integration variable x represents integrating over all α' , or $(\bar{\alpha} + \bar{\beta}d)$. The equivalence of Eq. (5.1) and Eq. (5.2) is a particularly important result, since in radiotherapy, constant dose per fraction is a common occurrence, and this allows specific treatment of heterogeneity in both α and β , without any assumption of correlation between the two, using a single integration. Due to the importance of this result, a formal proof of the equivalence of Eq. (5.1) and (5.2) is provided in Appendix C.

5.1.2 Clinical data

Outcome from three mature prostate cancer data sets was modeled. The first is a study by Stock,³⁴ who reports outcome for low dose rate permanent seed ¹²⁵I implants. The second and third are studies by Hanks³⁵ and Pinover³⁶, where outcome as a function of dose is recorded for conventional external beam therapy delivered at constant daily dose per fraction. The Stock data is stratified by PSA (prostate specific antigen), with the patients in the study having PSA between 4 and 20 ng/ml, with 68% less than 10 ng/ml. The Pinover study was for patients with less than 10 ng/ml PSA, and Hanks was for patients with PSA ranging from 10 to 20 ng/ml. Summaries of the treatment dose response are provided in Tables 5.1 to 5.3, and shown in Fig. 5.1.

Table 5.1. Clinical outcome for low dose rate, permanent seed brachytherapy implants as reported by Stock. The number of successful outcomes is n ; the total number of patients treated is N . The uncertainty on $bNED$, σ_{bNED} was calculated by the current author assuming a binomial distribution for outcome.

D_T (Gy)	n	N	$bNED$	σ_{bNED}
90	14	26	0.538	0.098
110	10	12	0.833	0.108
130	21	27	0.777	0.08
150	23	24	0.958	0.041
170	40	45	0.888	0.047

Table 5.2. Clinical outcome for constant dose per fraction for PSA < 10 ng/ml as reported by Pinover. The number of successful outcomes is n ; the total number of patients treated is N . The uncertainty on $bNED$, σ_{bNED} was calculated by the current author assuming a binomial distribution for outcome.

D_T (Gy)	n	N	$BNED$	σ_{bNED}
70.67	119	163	0.73	0.035
72.78	224	261	0.86	0.021
77.34	57	64	0.89	0.039

Table 5.3. Clinical outcome for constant dose per fraction for PSA 10 - 20 ng/ml as reported by Hanks. The number of successful outcomes is n ; the total number of patients treated is N . The uncertainty on $bNED$, σ_{bNED} was calculated by the current author assuming a binomial distribution for outcome.

D_T (Gy)	n	N	$bNED$	σ_{bNED}
68.5	7	10	0.7	0.145
71.6	15	23	0.652	0.099
73.7	5	8	0.625	0.171
75.8	20	22	0.909	0.061
79	5	6	0.833	0.152

FIG. 5.1. Dose response data recorded by Stock, Pinover and Hanks. Numerical values are given in Tables 5.1 to 5.3.

5.1.3 Objective Function

To estimate parameters from the TCP model that best fit the data listed in Tables 5.1 to 5.3 the method of least squares was used:

$$\chi^2 = \sum \frac{[TCP(\alpha, \sigma, k) - bNED]^2}{\sigma_{bNED}^2}. \quad (5.3)$$

Here, TCP is the model prediction as a function of the LQ parameter α , its variance σ^2 , and k , the number of tumour clonogens; bNED stands for measured biochemical No Evidence of Disease, which corresponds to the use of the PSA test to determine outcome. It is calculated by evaluating the ratio of cases without PSA failure to all cases. PSA failure is normally defined as three consecutive increases in PSA after therapy.⁵² The variance in bNED, σ_{bNED}^2 , is calculated assuming the clinical data is distributed by a binomial distribution:

$$\sigma_{bNED}^2 = \frac{NP(1-P)}{N^2}. \quad (5.4)$$

N is the number of patients at a dose point, and P is the proportion of successful outcomes, denoted bNED in Tables 5.1 to 5.3. If it is assumed that the binomial distribution is approximately Gaussian and that the tumour control model is linear within the confidence interval of the parameters, the least squares function given with Eq. (5.3) follows the Chi-Squared distribution. This method facilitates the construction of confidence intervals for parameter estimates since standard errors can be obtained using the method of constant Chi-Square boundary.⁵³ The constant Chi-Square

boundary method must be used cautiously since it can significantly underestimate confidence intervals if its assumptions are not satisfied.

5.2 Results

5.2.1 Results of tumour control modeling for the heterogeneous (population averaged) model

The Monte Carlo method that is described in Appendix D was used to evaluate Eq. (5.2). In principle this integral could be evaluated numerically, the purpose of Appendix D is to demonstrate a method that can easily be expanded to a much more complex model, including other inter-tumour heterogeneity and also intra-tumour heterogeneity. A grid search was used to minimize Eq. (5.3) applied to the prostate cancer clinical data given in Tables 5.1 to 5.3 and Eq. (5.2). It was found that the best estimates of $\bar{\alpha}$ and σ , when plotted as a function of $\ln(k)$ form a linear relationship that has often been observed in tumour control modeling with a heterogeneous model for other diseases.^{20,50,51} The parameter estimates for early stage prostate cancer, along with the χ^2 statistic plotted as a function of $\ln(k)$, are shown graphically in Fig. 5.2. The search method employed an initial coarse parameter search over a fixed $\ln(k)$ space using 1000 samples in the Monte Carlo, and a fairly large step size ($\Delta\alpha = 0.01$, $\Delta\sigma = 0.03$), so as to establish the approximate region of the linear relation. Subsequently, a fine search was performed over a parameter region limited to within 20% of the linear

FIG. 5.2. Parameter estimates for Eq. (5.3) using the Monte Carlo tumour control model described in Appendix D and the clinical data of Stock, Pinover and Hanks. The confidence intervals were constructed using the constant Chi-Square boundary technique using $\Delta\chi^2 = 5.99$ for two free parameters ($\ln(k)$ was held fixed) and 95% confidence limit.

regions found in the coarse search using 1,000,000 samples in the Monte Carlo, and reduced grid spacing. The confidence intervals were constructed by finding the region where χ^2 is less than $\chi^2_{\min} + Q\gamma$, and $Q\gamma = 5.99$ for two free parameters and 95% confidence interval.⁵⁴ The confidence interval in α was determined by holding $\ln(k)$ constant, and letting $\bar{\alpha}$ and σ vary freely whereas the confidence intervals in σ were obtained by holding both $\ln(k)$ and $\bar{\alpha}$ constant and varying only σ . Due to the nature of the solution space the confidence intervals are not symmetric, particularly for the Pinover and Hanks estimates. At $\ln(k) = 0$ there were no parameters that fell within the 95% confidence interval for all three plots in Fig. 5.2, and so none are reported for these values of $\ln(k)$. The upper end of $\ln(k)$, 23, was chosen arbitrarily since this corresponds to the largest number of cells (10^{10}) that can reasonably make up a tumour of about 10 cm^3 assuming a cellular density of $10^9/\text{cm}^3$. Had parameter searches been performed above $\ln(k) = 23$, the linear confidence region would be extended. The plots of α and σ in Fig. 5.2 show some up-down variation from the linear relation. This is attributed to the statistical variation of the Monte-Carlo calculation and also to the finite step size used in the parameter search.

5.2.1.1 Effect of non-linearity of the model

The method that was used to construct the confidence intervals on $\bar{\alpha}$ and $\bar{\alpha}'$ of Fig. 5.2 is called the method of constant χ^2 boundary; it is well described in Press.⁵³ This method is only valid in the case where the measurement errors (in this case the values in column 5 of Tables 5.1 to 5.3) are distributed as a Gaussian function and the model is linear in its parameters. In the present case the measurement errors are distributed as a binomial function. Under certain circumstances, the binomial distribution closely resembles a Gaussian distribution; however, many of the dose points in the present clinical data are close to bNED (the probability of success of the treatment) equal to one, and in this case, the binomial distribution is truncated at one, so the assumption of Gaussian distributed errors is not adequate. Furthermore, the model we are using, Eq. (5.2), is a double exponential that is convolved with a Gaussian function. This model is not linear in its parameters, nor can it be transformed into a linear model without using a complicated parameter substitution. (This is discussed in Chapter 6.) As well, simple inspection of Fig. 5.2 shows that the confidence intervals for α and α' are not symmetric, indicating that the distribution of α and α' estimates is not Gaussian. Since these estimates must be used to form estimates of the α/β ratio, it would be necessary to know their distribution in order to properly propagate uncertainties from the α and α' estimates to uncertainties in the α/β estimate. Finally, the final result involves propagating errors through a division by β , where the error on

β is on the order of β . This is a well-known situation where standard error propagation is problematic.

To verify the confidence limits given in Fig. 5.2, and to facilitate the propagation of error through the final α/β result, a Monte Carlo method of error analysis is used. The specific method is given in Appendix E, and it was derived from the method described by Press.⁵³ Briefly, the method involves generating computer-simulated random clinical data that follow the binary distributions defined by columns two and three in Tables 5.1 to 5.3. For each new set of simulated clinical data, Fig. 5.2 is reproduced. If this is done many times (5000 in this case), the result will be a distribution of α and σ estimates for each $\ln(k)$. The confidence interval is constructed directly from the distribution of parameter estimates. The tumour control model of Appendix D was replaced by numerical integration to verify Appendix D, and to speed up the computational time. The results analogous to Fig. 5.2 using the Monte Carlo error analysis are shown in Fig. 5.3(a). Fig. 5.3(b) is a plot of the quantity H , which is defined as σ/α . Its importance is discussed in the next chapter. The distribution of χ^2 is given in Fig. 5.3(c). Figures 5.2 and 5.3 agree well in parameter estimates, but it is apparent that the confidence intervals estimated by the method of constant Chi-Square boundary are underestimated, particularly for the Pinover and Hanks clinical data.

FIG. 5.3(a). Parameter estimates for Eq. (5.3). using a numerical integration for the heterogeneous tumour control model, Eq. (5.2) and the clinical data of Stock, Pinover and Hanks. The confidence intervals were generated by a Monte Carlo technique that is described in Appendix E.

FIG. 5.3(b). Estimate of the parameter σ/α derived from the data in Fig. 5.3(a) for the three published data sets used this study. The errors bars represent the 95% confidence intervals, and were generated using the Monte Carlo method of Appendix E.

FIG. 5.3(c). The distribution of χ^2 obtained for Fig. 5.3(a) and 5.3(b).

5.2.2 Results of tumour control modeling for the homogeneous model

To investigate the effect of heterogeneity on parameter estimates, the homogenous model, given by Eq. (3.3), was also used to estimate radiobiological parameters from the clinical data given in Tables 5.1 to 5.3. Error estimates were generated using Appendix E. The results are given in Figures 5.4(a) and 5.4(b). The same linear relation that was found in the homogenous case was also found for the heterogeneous case. This was unexpected since there are no other published results for the homogenous model that indicate a correlation of parameters which extend over a large region of $\ln(k)$. The reason for the large range of $\ln(k)$ in Fig. 5.4(a) where statistically meaningful α and α' estimates were obtained is because of the method of error analysis used. When the constant Chi-Square boundary method was used to obtain confidence intervals for the homogenous model, the result was a reduced range of $\ln(k)$ where statistically meaningful parameters existed. However, because the constant Chi-Square boundary method is inappropriate to this model, the result is that the range of $\ln(k)$ where parameter estimates are statistically meaningful is much larger than would be obtained using the constant Chi-Square method. To illustrate this Fig. 5.4(b) shows the minimum and maximum values of 95% of χ^2 values obtained from the synthetic data used in the error estimate method. If Eq. (5.3) applied to the homogeneous model followed the Chi-Squared distribution, 95% of the parameter estimates should fall within 3.84 of the minimum χ^2 . The range shown in Fig. 5.4(b) is considerably larger than this, and so in order to obtain the true 95% confidence limit

FIG. 5.4(a). Estimates and 95% confidence intervals of the α and α' parameters obtained when fitting to the same clinical data as Figures 5.2 and 5.3 using the homogeneous model, Eq. (3.3).

FIG. 5.4(b). The distribution of χ^2 obtained when plotting Fig. 5.4(a).

the constant χ^2 line that should be used for the homogeneous model is much larger than the tabulated values, which explains the large region of $\ln(k)$ observed in Fig. 5.4.

5.2.3 Combination of parameter estimates to obtain an estimate of the α/β ratio

In principle, there is no intrinsic reason not to use two separate dose response studies to estimate radiobiological parameters. There are technical difficulties such as establishing equivalent pre-treatment conditions such that the dose response established by a first treatment technique is the same response as the second technique. The Hanks and Pinover data cannot be directly combined with the Stock data since it is very difficult to establish if the pre-treatment conditions (number of tumour clonogens and radio-sensitivity) of the three patient groups are equivalent. Since the patient populations in the Stock study were from geographically different locations from the Pinover and Hanks studies, and since the numbers of patients in the studies were relatively low, (not in the thousands as one would like for a good statistical sample) it is most likely that the mean radiosensitivity between Stock and Pinover or Hanks is not equal. Further, the stem cell numbers are quite likely to be unequal since the PSA ranges for the clinical data do not coincide: the PSA range for the Stock study is 4 to 20 ng/ml with 68% being less than 10ng/ml, while the Pinover and Hanks studies are segregated by PSA with Pinover having all patients less than 10ng/ml and Hanks having all patients between 10 and 20 ng/ml. Finally, there is also an issue with the

relative biological effectiveness (RBE) of ^{125}I due to the possibly non-unity RBE of the low energy photons emitted by ^{125}I . The RBE of ^{125}I is a current area of research.^{40,41,44}

In the absence of better clinical data, however, it is justifiable to combine these studies if it is understood that the resulting α/β estimates may have biases due to unavoidable difficulties with the data. The benefit of such an exercise is that it gives some idea of how the α/β estimates vary depending on unknown quantities, such as $\ln(k)$ or α . The effect of heterogeneity can also be investigated by comparing results of the heterogeneous method, Fig. 5.3(a), with the results of the homogeneous method, Fig. 5.4(a). The only study on the effect of heterogeneity on parameter ratios is Dubray,⁵⁵ which was written before the idea of obtaining radiobiological parameter estimates from clinically measured dose response data was considered seriously. Brenner,⁵⁶ Fowler,³⁹ and King⁵⁷ have previously used a similar practice to estimate the α/β ratio for prostate cancer.

Assuming that the clinical data given in Tables 5.1 to 5.3 is suitable for estimating the α/β ratio, the data from low dose rate and external beam therapy can be combined by determining β from α' and α for a fixed $\ln(k)$. Since $\bar{\alpha}' = \bar{\alpha} + \bar{\beta} d$, the formula for $\bar{\alpha} / \bar{\beta}$ is

$$\frac{(\bar{\alpha})}{(\bar{\beta})} = \frac{\bar{\alpha} d}{(\alpha' - \bar{\alpha})}. \quad (5.5)$$

Some discussion regarding the meaning of the quantity α/β in Eq. (5.5) is required due to the heterogeneous nature of the analysis. In Eq. (5.5) the bar over α and β was introduced to specify that they represent the mean value of these quantities in a population of patients, each patient having unique α and β . Hence, by fitting Eq. (5.2) to clinical data, the resulting estimates of the quantities we wish to fit to the clinical data, $\bar{\alpha}$, and $\bar{\alpha}'$, are the population means of α and α' . The $\bar{\alpha}/\bar{\beta}$ quantity in Eq. (5.5) is thus a ratio of mean values of α and β that are found in the population. In the remainder of this chapter, the symbol α/β represents this ratio of mean values.

The α/β ratio is plotted in Figures 5.5(a) and 5.5(b) using Eq. (5.5). In both the (a) and (b) parts of the figure the α/β ratio is plotted by comparing the results of Stock to either Pinover (the low PSA, less than 10 ng/ml) or Hanks (the intermediate PSA, 10 – 20 ng/ml). This was done because the Stock data covered both ranges of PSA (4 – 20 ng/ml). The error bars on these plots represent 95% confidence intervals, and were determined using the Monte Carlo method given in Appendix E. The Monte Carlo error propagation was used since it was used to obtain confidence limits on $\bar{\alpha}$ and σ ; it was a simple extension of this method to obtain confidence intervals for α/β .

FIG. 5.5(a). Plots of the α/β ratio as a function of $\ln(k)$ using the homogeneous fit results given in Fig. 5.4(a). The error bars represent 68.3% (innermost), 90% (middle) and 95% (maximum) confidence intervals as evaluated using the Monte Carlo method of Appendix E.

FIG. 5.5(b). Plots of the α/β ratio as a function of $\ln(k)$ using the heterogeneous fit results given in Fig. 5.3(a). The error bars represent 68.3% (innermost), 90% (middle) and 95% (maximum) confidence intervals as evaluated using the Monte Carlo method of Appendix E. This figure is of the same quantity as for Fig. 5.5(a), except heterogeneity was added to the model of tumour control.

5.3 Discussion

The goal of this chapter was to use a heterogeneous tumour control model to investigate the dependence of the α/β ratio on assumed inter-tumour heterogeneity. This is important because it is tempting to use the homogeneous model to extract parameters since this model is particularly easy to implement. The justification for using low heterogeneity in tumour control models is supported by the work of Dubray,⁵⁵ who argued that the ratio of parameters should be stable despite differing heterogeneity of parameters. This issue is also discussed by Fowler, who asked whether there would simply be a constant shift to higher values in individual parameters (keeping a constant parameter ratio) if their values were estimated using a heterogeneous method.³⁹ As well, there are several recent papers that do propose a low value for the α/β ratio of prostate cancer based on clinical modeling using the homogenous model.^{14,39,42,48,57} In the radiation oncology literature, this low value of the α/β ratio is being increasingly quoted as a justification for hypofractionation of prostate cancer, so a fresh examination of the impact on the α/β ratio using the heterogeneous tumour control model is required.

The most striking feature of the principal result, Fig. 5.5, is the size of the 95% confidence intervals, and also the difference in confidence intervals between the heterogeneous and homogeneous solution. These results indicate that the constant Chi-

Square method of determining confidence intervals can significantly underestimate the confidence intervals for the types of data and model considered here. This is shown in Figs. 5.3(c) and 5.4(b), which show the range of Chi-Square containing 95% of parameter estimates. If Eq. (5.3) followed a Chi-Squared distribution, this range would be 3.84 and 5.99 for the homogeneous and heterogeneous models, whereas in Figs 5.3(c) and 5.4(b), this range is no less than 13 and in some instances, greater than 30.

For the heterogeneous model, however, the actual size of the confidence intervals are significantly larger than for the homogeneous model, and due to the asymmetry in the confidence intervals (the large tail in distributions of α/β estimates), the 95% confidence interval for the heterogeneous model is significantly larger than the 68.3% interval (i.e. the 95% confidence interval is greater than 2 standard errors). In fact, the 95% confidence interval is so large that one cannot give an α/β estimate using the heterogeneous model with any statistical significance. This implies that the specifications required of the clinical data for the heterogeneous model to yield a statistically significant result are much tighter than presently available from published data. Further, comparison of the homogeneous to heterogeneous α/β estimates indicates that the use of the homogeneous model may appreciably overestimate the statistical significance of the result. This result is somewhat intuitive since adding an extra degree of freedom to the model, by including heterogeneity, will naturally extend the range of parameter estimates. Fig. 5.5 shows that this extension of the confidence interval is an important consideration in the estimation of the α/β ratio.

Due to the size of confidence intervals for the heterogeneous estimates, it is difficult to compare differences between α/β estimates with homogeneous and heterogeneous models. However, if the confidence intervals are ignored, the two models yield similar estimates for α/β as a function of the number of clonogens. At high $\ln(k)$ the homogeneous estimates are consistently about 95% of the heterogeneous estimates. This ratio drops to not less than 75% at low $\ln(k)$. Thus, heterogeneity does not appear to greatly affect the value of the α/β estimate, which agrees with the conclusions of Dubray,⁵⁵ and assumptions made by Brenner.^{38,58} However, this equivalence is effectively nullified since the homogeneous (individual) tumour control model significantly underestimates the confidence intervals of the α/β parameter estimate.

Chapter 6

THEORETICAL CONSIDERATION FOR POPULATION HETEROGENEITY IN TUMOUR CONTROL MODELING

In Chapter 5 it was shown that modeling clinical data using the heterogeneous tumour control model did not yield a most significant parameter estimate. Instead, it yielded a linear correlation of parameter estimates between $\bar{\alpha}$ and $\ln(k)$ and σ and $\ln(k)$. This almost perfectly linear correlation has also been shown to exist for other cancers, as reported by other investigators.^{20,50,51} Any evidence of linearity is intriguing since it is not evident from the outset that Eq. (5.2) has linear properties. The purpose of this chapter is to provide a theoretical explanation for this result, to investigate the physical meaning of the parameter correlation between $\bar{\alpha}$ and $\ln(k)$, and to explain the large confidence intervals given in Fig. 5.5(b). Sections 6.1 and 6.3 along with Chapter 5

make up my first publication.⁴⁹ Section 6.4 is an extract of my second publication.⁵⁹

6.1 Parameter scaling of the heterogeneous tumour control model

The heterogeneous tumour control model, reduced to a single variable $\bar{\alpha}'$ was expressed in Eq. (5.2):

$$P \equiv \text{TCP} = \frac{1}{\sqrt{2\pi}\sigma} \int_{-\infty}^{\infty} \exp(-ke^{-x D}) \exp\left(-\frac{(x - \bar{\alpha}')^2}{2\sigma^2}\right) dx. \quad (5.2)$$

The variable k is the number of tumour clonogens, $\bar{\alpha}'$ is the radiosensitivity variable, and σ^2 is its variance. Making the substitutions:

$$u = xD - \ln(k),$$

$$\kappa = \bar{\alpha}' D - \ln(k),$$

$$A = \sigma D,$$

gives

$$P = \frac{1}{\sqrt{2\pi} A} \int_{-\infty}^{\infty} \exp\left(-e^{-u} - \frac{(u - \kappa)^2}{2A^2}\right) du. \quad (6.1)$$

The integration variable disappears upon performing the integration[†], so it can be seen that the tumour control probability, P , depends on two intrinsic, dimensionless

[†] The integration limits $-\infty$ to $+\infty$ allows negative α values, which we should not include in the integration. If σ/α is about 0.3, and α is limited to be positive, integrating Eq. (5.2) over all α produces a difference of about 4 parts in 10000 with the truncated integration. For σ/α less than 0.26, the difference is essentially nil, and for a maximum error of 1%, σ/α must be less than 0.429, which is likely beyond the clinical range. Thus, we are justified in using the integration limits given in Eq. (5.2). The benefit is

variables, κ and A . Mathematically, $P = f(\kappa, A)$. The physical interpretation of these variables is as follows. κ relates to $\overline{\alpha'} D$, which corresponds to the fraction of cell loss, and $\ln(k)$, which depends on the initial number of stem cells. Thus κ represents an effective number of tumour stem cells remaining after irradiation. The variable $A = \sigma D$ represents the variability of the number of tumour clonogens remaining after dose D was administered to a population of tumours. A plot of Eq. (6.1), which shows P as a function of the new variables κ and A , is shown in Fig. 6.1. Figure 6.1(a) shows a three-dimensional view of Eq. (6.1) with P plotted on the z-axis. Figure 6.1(b) shows isoTCP contour lines of the same function P . When κ is positive, the remaining number of tumour stem cells is small, and P approaches unity. When κ is small or negative, there are large numbers of remaining stem cells so the probability of tumour control decreases, and tends to zero as κ decreases. Plots of P vs. κ for fixed A yield a sigmoid shaped curve ranging from zero to one. As A increases, the slope of the sigmoid curves decreases, as expected with increasing heterogeneity. This formulation of the tumour control model uses physically important variables:

1. The logarithm of the mean number of stem cells that remain after treatment, κ .
2. The variation in the number of tumour clonogens remaining after dose D was administered to a population of tumours, A .

Parameter scaling has previously been discussed by Roberts²³ and by Fenwick.²⁰

that integrating over all space simplifies the theory since the integration variable is not a parameter in the final equations.

FIG. 6.1(a) A three-dimensional plot of tumour control probability given by Eq. (5.2), as a function of the new variables κ , and A .

FIG. 6.1(b) Contour plot of Fig. 6.1(a) in increments of 5%, starting at 5% for the leftmost isoline. For a large part of the parameter space, ($A = \sigma D > \sim 1$), the isolines are linear whose asymptotes all intersect the point $\kappa \approx 0.577$, $A = 0$.

Both approaches involve estimating the heterogeneous tumour control expression in a closed form. Roberts approximated the model for both low and high heterogeneity. He approximated the low heterogeneity case by observing that the Gaussian term in Eq. (5.2) would have a narrow peak for small σ , and then expanded the double exponential in a linear approximation and integrated over limits defined by the narrow peak of the Gaussian term. For high heterogeneity, Roberts treated the double exponential as a Heaviside step function, and so the tumour control model is then expressed as the complimentary error function, where the lower limit of integration is the mean value of radiosensitivity. The high heterogeneity form of the Roberts model was evaluated by Stavrev,⁶⁰ and found not to be very useful in estimating parameters. Fenwick also obtained a closed form of the heterogeneous tumour control model. His approach was to expand the heterogeneous tumour control function in a Taylor series, but found the series did not converge well unless the equivalent of the κ parameter is greater than 3. His solution was to split the integral into two parts, which are evaluated separately, and he shows that a maximum error can be achieved by keeping four terms in the Taylor series. Even so, the series does not converge well for σD less than 1. The parameter scaling used here is different than these two approaches since the final expression is not a closed form solution, and the scaled variables, κ and A , are not independent as they both depend on the dose D . This choice of variables, and the interdependence has useful qualities that are demonstrated in Section 6.2.

6.2 The meaning of the slope of the α vs. $\ln(k)$ parameter estimates

The purpose of this section is to show that the reciprocal slope of the α vs. $\ln(k)$ parameter correlation that is obtained using a heterogeneous (population) tumour control model is an estimate of the dose of 50% tumour control for the clinical data provided. This is accomplished by extending the theory of parameter scaling introduced in Section 6.1. In this section, it is shown how this re-parameterization renders linear the heterogeneous tumour control model, Eq. (5.2). Making the assumption that the linearity holds over a wide range of the $\overline{\alpha'}$, σ , and $\ln(k)$ parameters, unscaling the model leads to a procedure that can construct parameter estimates for $\overline{\alpha'}$ and σ as a function of $\ln(k)$ without using any type of statistical test, such as Eq. (5.3). In other words, the following procedure allows parameters to be fit to the heterogeneous tumour control model without the need to assume which statistical test is best (least squares, minimum modulus, maximum likelihood, or others), since no statistical test is used. This is a significant development since the credibility of parameter estimation is increased if any statistical assumptions are removed. There is also an important increase in the computational efficiency of the parameter estimation method. By demonstrating a procedure that produces the same linear correlation of $\overline{\alpha'}$ and $\ln(k)$ parameters, it is shown that the reciprocal slope of this relationship is equal to dose of the 50% TCP point.

6.2.1 A direct procedure to obtain parameters for the heterogeneous tumour control model

Equation (5.2) was transformed into a dimensionless model, Eq. (6.1) by introducing the scaling parameters $\kappa = \bar{\alpha}' D - \ln(k)$, and $A = \sigma D$. These two variables are not independent as they both depend on the dose D . This offers a convenient method of evaluating Eq. (5.2) for any general case: evaluate Eq. (6.1) as a function of κ and A and create a look-up-table. Convert the variables $\bar{\alpha}'$, σ and $\ln(k)$ to the scaled variables κ and A for each dose point on the survival curve, and determine the value of the tumour control probability by looking up its value in the look-up-table. In doing so, it is evident that the function given in Eq. (5.2) can be evaluated by determining the values of the P surface that intersects a straight line in the κ - A space. The relationship for the line in κ - A space is obtained by isolating D from the scaled parameters. From the scaling of σ , $D = A/\sigma$. Substituting this into the formula for κ yields the formula:

$$A = \frac{\sigma}{(\bar{\alpha})} [\kappa + \ln(k)] = H [\kappa + \ln(k)]. \quad (6.2)$$

The variable H is introduced as the ratio of σ to $\bar{\alpha}$. In the κ - A space, the tumour control probability function given by Eq. (5.2) will be the surface given by Eq. (6.1) evaluated along the line given by Eq. (6.2). This line has slope equal to $\sigma/\bar{\alpha}'$ and intercept on the κ axis equal to negative $\ln(k)$. An illustration is given in Fig. 6.2(a),

FIG. 6.2(a). Tumour control probability as a function of dose data used to illustrate the procedure for estimating radiobiological parameters given in Section 6.2. These points were generated with $\bar{\alpha} = 0.16 \text{ Gy}^{-1}$, $\sigma = 0.04 \text{ Gy}^{-1}$, and $\ln(k) = 10$ using the Monte Carlo method to evaluate tumour control given in Appendix D.

FIG. 6.2(b). The data used to plot Fig. 6.2(a) plotted in the κ - A parameter space.

which shows a TCP function for the parameters $\overline{\alpha'} = 0.16 \text{ Gy}^{-1}$, $\sigma = 0.04 \text{ Gy}^{-1}$, and $\ln(k) = 10$, and in Fig. 6.2(b) which shows the same plot in the κ - A space.

By scaling the variables $\overline{\alpha'}$, σ and $\ln(k)$, the non-linear function, Eq. (5.2), was transformed into a linear response, Eq. (6.2). This allows the possibility of using linear regression to obtain parameter estimates from clinical data. For instance, the following procedure could be used:

1. Generate a look-up-table of TCP by numerically integrating Eq. (6.1) as a function of κ and A .
2. Choose a parameter σ .
3. Convert each measured dose response point to an A value by multiplying the dose by σ .
4. For each A value, determine κ by interpolating the look-up-table generated in step 1 along fixed A to find the known (measured) TCP value at each dose. This produces a set of κ - A coordinates.
5. Repeat steps 2 – 4 for many σ .
6. Choose the best σ by determining which set of κ - A coordinates found in step 4 forms the most linear relationship.
7. Determine $\overline{\alpha'}$ by dividing the value of σ found in step 6 by the slope of the line for σ of step 6.
8. Determine $\ln(k)$ from the x -intercept of the line found in step 6.

The above method forms the basis of a method that should, in principle, determine which point in the $\overline{\alpha'}$ vs. $\ln(k)$ linear confidence region is the most likely parameter estimate.

This method was applied to the data shown in Fig. 6.2(a), which is nearly noiseless data since it was generated using the Monte Carlo method of Appendix D with 1,000,000 samples. Fig. 6.2(c) shows the series of coordinates found in step 4 plotted in the κ - A space. The lowermost set of coordinates was for $\sigma = 0.01$. Each set of coordinates was constructed by increasing σ by 0.01, up to the top line which is for $\sigma = 0.15$. By simple visual inspection, it can be seen that each set of κ - A coordinates formed for all σ , forms a near linear relationship. Close inspection of Fig. 6.2(c) reveals that the fourth curve from the bottom, constructed from the true σ , is in fact the only truly linear line. This is seen from the bottom graph of Fig. 6.2(d). The curves below it are all slightly concave upward; the curves above it are all slightly concave downward. The amount of curvature is minimal, and so the method suggested to estimate the optimal $\overline{\alpha'}$, σ and $\ln(k)$ parameter has an important flaw since it will only work for absolutely perfect clinical data: data that has no noise component. Data that is obtained from a clinical dose escalation trial normally has more noise associated with it, and so this would prohibit the above method from working since this noise would make the most linear set of κ - A coordinates indistinguishable from all other sets. A different manner of thinking about Fig. 6.2(c) is that this figure shows that the linearity

FIG. 6.2(c). The sets of κ - A parameter coordinates obtained using the procedure outlined in Section 3.3 and the data given in Fig. 6.2(a). The lowest set was constructed using $\sigma = 0.01 \text{ Gy}^{-1}$; the highest set was made with $\sigma = 0.15 \text{ Gy}^{-1}$. The fourth set from the bottom was constructed from the true σ , 0.04 Gy^{-1} , and this is the only set of coordinates that forms a perfect linear relationship.

FIG. 6.2(d). Parameter estimates obtained using the extension to the procedure given in Section 6.2 and the pseudo-clinical data given in Fig. 6.2(a). The top graph is the quantity $H = \sigma/\alpha$, which is the slope of each set of κ - A coordinates from Fig. 6.2(c) plotted against the negative x -intercept, $\ln(k)$. The middle graph is the value of σ used to construct each set of κ - A coordinates in Fig. 6.2(c) divided by the slope of the coordinates (σ/α) plotted against the negative x -intercept, $\ln(k)$. The bottom plot shows the deviation of each curve in Fig. 6.2(c) from linearity by plotting the sum of the deviations from the best-fit line squared for each set of κ - A parameters in Fig. 6.2(c).

achieved by transforming data in Fig. 6.2(a) through the scaled variables κ and A and Eq. (6.2) appears to hold over a large range of parameters. This provides a physically satisfying explanation for the observation that a linear set of $\overline{\alpha'}$ and $\ln(k)$ parameters can be made to fit Eq. (5.2) equally well. A set of radiobiological parameters can be constructed from Fig. 6.2(c) making only one important assumption. Let us assume that the linearity of κ - A coordinates obtained by applying the scaling procedure outlined above holds for an infinite set of parameters. In other words, let us assume that Eq. (6.2) applies equally to each set of κ - A coordinates shown in Fig. 6.2(c). With this assumption, the procedure outlined above can be unscaled by applying Eq. (6.2) to each line in Fig. 6.2(c): determine an $\overline{\alpha'}$ for each line by dividing the σ used to construct the line by its slope, and $\ln(k)$ by finding the x -intercept of the line. Using this method to unscale Fig. 6.2(c), Fig. 6.2(d) was generated. The top graph shows the plot of $H = \sigma/\overline{\alpha'}$ vs. $\ln(k)$, the middle graph is the plot of $\overline{\alpha'}$ vs. $\ln(k)$, and the bottom graph shows the least squares statistic of each of the fifteen lines in Fig. 6.2(c). This bottom graph is included to show that the line constructed for $\ln(k)$ equal to 10, which is the true value, has no deviation from a perfectly linear relationship. The middle graph shows the well-known linear relationship between $\overline{\alpha'}$ and $\ln(k)$ estimates for the heterogeneous (population) tumour control model. The most important consequence of Fig. 6.2(d) is that the linear relationship between $\overline{\alpha'}$ and $\ln(k)$ parameters was obtained directly from scaling; no statistical tests were used to determine these parameter estimates. This is a significant development since any parameter estimate obtained by statistical analysis can be criticized on the basis of the assumptions used in forming the

statistical test. A method that can estimate parameters without statistical assumptions adds credibility to the parameter estimates and confidence intervals.

6.2.2 Slope of α vs. $\ln(k)$ parameter estimates

The scaled parameters can be used to show that the slope of the $\overline{\alpha'}$ vs. $\ln(k)$ linear confidence region is equal to the reciprocal of the dose of 50% tumour control. To show this, consider two lines on Fig. 6.2(c), line i and line j . Keeping the assumption that the linearity of κ - A coordinates is independent of scaling, and further assuming that the slope of each line is the same[‡], $H = \sigma_i / \overline{\alpha'_i}$ is the same for all i . Since the x -intercept is $\ln(k)_i$:

$$\overline{\alpha'_i} = \frac{\sigma_i}{H}, \quad \overline{\alpha'_j} = \frac{\sigma_j}{H},$$

$$\ln(k)_i = \frac{A(\kappa=0)_j}{H}, \quad \ln(k)_j = \frac{A(\kappa=0)_j}{H}.$$

The slope of the $\overline{\alpha'}$ vs. $\ln(k)$ line will be $(\overline{\alpha'_i} - \overline{\alpha'_j}) / [\ln(k)_i - \ln(k)_j]$.

$$\Delta \overline{\alpha'} = \frac{\sigma_i - \sigma_j}{H},$$

$$\Delta \ln(k) = \frac{A(\kappa=0)_i - A(\kappa=0)_j}{H}.$$

[‡] This assumption is not valid at low A (when A is less than 1, see Fig. 6.2(d), top graph). At larger A , this assumption can be verified by approximating the iso-TCP lines of Fig. 6.1 as linear and intersecting at the point $A = 0$ and $\kappa \sim 0.577$. In this region, A is approximately proportional to κ , the proportionality constant depending on the iso-TCP line. Due to this property, it can be shown that adjacent lines of Fig. 6.2(c) are approximately parallel at $A > 1$.

The slope of the $\overline{\alpha'}$ vs. $\ln(k)$ plot is then:

$$\text{slope} = \frac{\sigma_i - \sigma_j}{A(\kappa=0)_i - A(\kappa=0)_j}. \quad (6.3)$$

To calculate the difference between the A intercept of lines i and j , from Fig. 6.2(c) it is evident that the iso-TCP line for 50% TCP is approximately parallel to the A axis for most of the κ - A space ($A > 1$). Thus, the difference between A intercepts of lines i and j is the difference between A values at 50% TCP. Substituting this into Eq. (6.3):

$$\text{slope} = \frac{\sigma_i - \sigma_j}{\sigma_i D_{50} - \sigma_j D_{50}} = \frac{1}{D_{50}} = \text{constant}.$$

This justifies the interpretation of the quantity D determined from linear regression of linear confidence regions in the $\overline{\alpha'}$ vs. $\ln(k)$ space as representing a unique physical dose, and shows that this quantity is an estimate of the dose of 50% TCP.

To justify the assumptions made in formulating the above theory, the correspondence of parameter estimates obtained when using the method I have described with another accepted method of estimating parameters is established. A series of simulations on computer-simulated data were performed using both the method of parameter scaling, and using the method of maximum likelihood to estimate parameters. In order to test this procedure under general conditions, clinical data that corresponds to a wide range of parameters was needed. To obtain these, computer-simulated data according to Eq. (5.2) was generated using the Monte Carlo method of Appendix D. The Monte Carlo computer-generated pseudo clinical data is binary, as is real clinical data, so the

binomial distribution was used to formulate the maximum likelihood statistic. The most likely estimates for $\overline{\alpha'}$ and σ were generated as a function of $\ln(k)$. The likelihood function, L , is constructed by writing the total probability of observing N_{cured} patients for N_{pat} total samples in the Monte Carlo. Using the binomial distribution, this is written

$$L(\alpha, \sigma) = \prod_{i=1}^{\text{\#dose points}} \binom{N_{\text{pat}_i}}{N_{\text{cured}_i}} P_i(\alpha, \sigma)^{N_{\text{cured}_i}} (1 - P_i(\alpha, \sigma))^{N_{\text{pat}_i} - N_{\text{cured}_i}} .$$

The function P is the tumour control function given in Eq. (5.2). As is customary, the logarithm of the likelihood function was minimized. This is the sum of the logarithm of the three individual terms taken over all dose points. The first term, the number of combinations term, does not depend on parameters that are being minimized, and so it was omitted from the likelihood function.

To observe a wide spectrum of response (and expecting the slope of the α vs. $\ln(k)$ curve to vary as the inverse of the dose of 50% TCP) three general cases where the dose of 50% response was 40, 60, and 80 Gy were simulated (for simplicity, β was taken to be 0, so $\overline{\alpha'} = \overline{\alpha}$). For each category, differing heterogeneity was simulated by letting $\sigma/\overline{\alpha}$ vary from 0.05 to 0.3 in steps of 0.05. This was done for a fixed value of $\ln(k)$ equal to 20. For all cases the dose response was simulated between 10% and 90% with seven evenly spaced TCP points. These results are shown in Fig. 6.3. Fig. 6.3(a) shows the effect of varying H ($\sigma/\overline{\alpha}$). It plots the estimates of $\overline{\alpha}$ at the true value of $\ln(k)$ (equal to 20) for each of the three baseline TCP curves. To verify the

remaining part of the $\bar{\alpha}$ vs. $\ln(k)$ plot, Fig. 6.3(b) shows the inverse of the slope of the $\bar{\alpha}$ vs. $\ln(k)$ plot as a function of $\sigma/\bar{\alpha}$ for the three baseline TCP curves. The value of the dose of 50% TCP is included as a dotted line in each of these plots, and it is seen to agree very well with the inverse slope of both methods. Finally Fig. 6.3(c) shows results for the estimate of σ (at the true $\ln(k)$, 20) for the three baseline TCP curves. Fig. 6.3(c) includes 6 sub-plots for each set of heterogeneity simulated. The true value of heterogeneity is also included in Fig. 6.3(c).

In general, the numerical value of the parameter estimates for both methods are in excellent agreement, which justifies the assumptions made above. In certain cases, the method of parameter scaling did not yield an estimate for either the $\bar{\alpha}$ or σ parameter at the true value of $\ln(k)$ for these simulations, which is 20. These are for cases where $\bar{\alpha}$ is low and H is also low, i.e. for the simulations when D_{50} is 60 or 80 at $H = 0.05$. In this case the modeling is in the region of the κ - A space that is close to the origin, where the iso-TCP lines deviate considerably from linearity; the assumption of scaling invariance is not valid. In the case where $\ln(k)$ or $\bar{\alpha}$ are small, the modeling will be in this region and is not reliable using the procedure I have developed here. This is shown in Fig. 6.3(a) and 6.3(c) where the parameter scaling method produces no estimate for α and σ at $H = 0.05$ and D_{50} of 60 or 80 Gy. This effect is also seen in Fig. 6.3(b) which shows some discrepancy between the slope of the α vs. $\ln(k)$ plot and the D_{50} value. This is due to the changing slope at low A (low $\ln(k)$) in the non-linear region of the A vs. κ plot.

FIG. 6.3(a). Comparison of parameter estimates obtained using the method of parameter scaling with the method of maximum likelihood. Top: a dose response for an LDR treatment was constructed with a dose of 50% tumour control of 40 Gy and using $\ln(k)$ equal to 20. α estimates evaluated at $\ln(k)$ 20 are plotted, with 95% confidence intervals, for dose response constructed with H (σ/α) = 0.05 to 0.3. The true value of α is plotted as a dotted line. Middle and bottom: similar parameter estimates for α as obtained for the top plot, but with the 50% dose equal to 60 Gy, and 80 Gy.

FIG. 6.3(b). Comparison of estimates for the inverse slope of the α vs. $\ln(k)$ plot using the method of parameter scaling and the method of maximum likelihood. Top plot: $D_{50} = 40$, middle: 60 Gy, bottom: 80 Gy. For each plot H was varied from 0.05 to 0.3. The true values are also plotted as a dotted line.

FIG. 6.3(c). Comparison of estimates for σ using the method of parameter scaling and the method of maximum likelihood. The value of σ plotted is at the value for $\ln(k) = 20$ for the three D_{50} values (plotted on x-axis), for $H = 0.05$ (top left) to 0.3 (bottom right). The true value of H is shown as a dotted line. As for Fig. 6.3(a), the method could not estimate a value for H when the true H is low, and D_{50} is large.

6.3 Expressions for the α/β ratio using scaled parameters

The parameters κ and A that were introduced in Section 3.1 have the benefit of providing physical insight into the tumour control model. In this section, new formulas for the α/β ratio are developed using these parameters. The purpose is to develop formulas that allow physical interpretation of the modelling results that are more intuitive than Equation (5.5).

In the following (and for the remainder of the chapter) the subscripts b and e are used to denote brachytherapy (b) and external beam therapy (e). The linear relationship between $\overline{\alpha'}$ and $\ln(k)$ can be described by the formula for κ ,

$$\kappa = \overline{\alpha'} D - \ln(k).$$

Making the assumption[§] that a single value of a physical dose characterizes this equation and that there is a physical interpretation for the associated value of κ , these parameters can be used to form further relationships. The estimate for κ from brachytherapy provides a linear relationship between $\overline{\alpha'}$ and $\ln(k)$ given by

$$(\overline{\alpha'})_b D_b - \ln(k) = \kappa_b.$$

The estimate for κ from external beam therapy gives

[§] This assumption was justified in Section 6.2.

$$(\overline{\alpha'})_e D_e - \ln(k) = \kappa_e .$$

For brachytherapy, $(\overline{\alpha'})_b = \overline{\alpha}$. In external beam therapy, $(\overline{\alpha'})_e = (\overline{\alpha} + \overline{\beta} d)$. Making these substitutions

$$\overline{\alpha} D_e - \ln(k) = \kappa_e , \quad (6.4)$$

$$(\overline{\alpha} + \overline{\beta} d) D_e - \ln(k) = \kappa_e . \quad (6.5)$$

To estimate the α/β ratio using low dose rate and external beam we must assume that the two treatment methods are applied to tumours with equivalent radiosensitivity and numbers of stem cells prior to treatment. Two methods are possible: we could equate Eqs. (6.4) and (6.5) either by isolating $\overline{\alpha}$, and generating an expression in terms of $\ln(k)$, or $\ln(k)$ can be isolated, and the α/β ratio can be determined in terms of $\overline{\alpha}$. Using the first method

$$\frac{(\overline{\alpha})}{(\overline{\beta})} = \frac{d D_e}{D_b \left(\frac{\kappa_e + \ln(k)}{\kappa_b + \ln(k)} \right) - D_e} . \quad (6.6)$$

Using the second method

$$\frac{(\overline{\alpha})}{(\overline{\beta})} = \frac{d D_e}{(D_b - D_e) - \frac{1}{(\overline{\alpha})} (\kappa_b - \kappa_e)} . \quad (6.7)$$

To show that these methods agree with Eq. (5.5), estimates for κ and D and, 95% confidence interval, that can be used in Eq. (6.6) were obtained by determining the mean slope and intercept of Fig. 5.3(a) and Fig. 5.4(a). These are given in Tables 6.1

and 6.2. A similar method of error analysis as given in Appendix E was used, where distributions of estimates for slope, intercept, κ and D were obtained by simulating synthetic data according to Tables 5.1 to 5.3. For each value of κ and D , a plot of α/β was made as a function of $\ln(k)$, the distributions of $\bar{\alpha}/\bar{\beta}$ were plotted to compare with the results in Fig. 5.5. The results for α/β are shown in Fig. 6.4; the agreement with Fig. 5.5 is excellent. This result is expected, since the $\bar{\alpha}$ and $\bar{\alpha}'$ values of Eq. (5.5) vary linearly with $\ln(k)$, and Eq. (6.6) simply uses this observation. The correspondence between α/β estimates plotted with Eq. (5.5) and (6.6) confirms that the correlation between $\bar{\alpha}$ and $\ln(k)$ is well represented by a linear function. Eq. (6.6) is more useful than Eq. (5.5) because it offers physical interpretation by employing a quantity D that represents physical dose. As shown in Section 6.2, this dose represents the dose of 50% tumour control. This allows the accuracy of the result to be evaluated since radiotherapy practitioners should have an intuitive knowledge of D_{50} . These implications are discussed in Section 6.5.1.

FIG. 6.4. The α/β ratio plotted using Eq. (6.6) and the values for κ and D given in Table 6.2.

Table 6.1. Linear Fits of Fig. 5.5(a) to α vs. $\ln(k)$ with 95% confidence intervals for fits using the homogenous model.

	Stock	Pinover	Hanks
κ	0.624	1.621	1.642
min	0.176	1.421	1.131
max	1.192	1.854	2.302
D	90.2	72.2	71.7
min	88.4	71.9	69.5
max	91.7	72.4	73.0

Table 6.2. Linear Fits of Fig. 5.5(b) to α vs. $\ln(k)$ with 95% confidence intervals for fits using the heterogeneous model.

	Stock	Pinover	Hanks
κ	0.592	1.290	1.207
min	0.430	0.699	0.628
max	0.875	1.850	1.949
D	84.2	69.5	67.4
min	70.0	54.1	48.8
max	93.6	72.5	72.7

6.4 Heterogeneous isoeffect analysis

Another expression for α/β can be derived using the parameter scaling introduced in this chapter. This is done using the idea of isoeffect analysis, but fully including heterogeneity. In the homogeneous case, an equation for α/β has been obtained by assuming that equivalent radiobiological effect (tumour control) obtained from different fractionation protocols is due to equivalent surviving fractions of cells. Using Eq. (2.22) to write the radiobiological effect for two equivalent exposures of

different total and fraction dose,

$$BED_1 = D_1 \left[1 + \frac{d_1}{\alpha/\beta} \right] = BED_2 = D_2 \left[1 + \frac{d_2}{\alpha/\beta} \right].$$

Isolating α/β gives

$$\frac{\alpha}{\beta} = \frac{d_2 D_2 - d_1 D_1}{D_1 - D_2}. \quad (6.8)$$

In the special case where subscript 1 refers to brachytherapy and 2 to external beam therapy, and using $d_l = d_b = 0$, Eq. (6.8) reduces to a well-known equation,⁵⁷

$$\frac{\alpha}{\beta} = \frac{d_e D_e}{D_b - D_e}. \quad (6.9)$$

Using a similar approach, the parameterization of Eq. (5.2) in the parameters κ and A also leads to a method of determining the α/β ratio that directly considers heterogeneity. The striking feature of Fig. 6.1(b) is that the curves of equivalent tumour control probability, or isoeffect curves are, over a large portion of the space plotted, linear in κ and A , with the exception being at low A ($A = \sigma D < \sim 1$). Making the assumption that over a clinically relevant region the isolines are linear we can write,

$$A = m\kappa + n, \quad (6.10)$$

where m and n are the slope and intercept of the isoline. If equivalent effects (survival) are obtained from a low dose rate treatment and from a fractionated external beam treatment, then the parameters κ and A from these treatments should fall on the same

isoline given by Eq. (6.10). Substituting the expressions for κ , A and keeping with the 'b' and 'e' subscript system of Section 6.3,

$$\kappa_b = (\bar{\alpha}')_b D - \ln(k), \quad (6.11)$$

$$\kappa_e = (\bar{\alpha}')_e D - \ln(k), \quad (6.12)$$

$$A_b = \sigma_b D, \quad (6.13)$$

$$A_e = \sigma_e D. \quad (6.14)$$

The parameters $(\bar{\alpha}')_b$ and $(\bar{\alpha}')_e$ have the same meaning as above. The standard deviation of $(\bar{\alpha}')_e$ is given by $\sigma_e = \sqrt{\sigma_\alpha^2 + d^2 \sigma_\beta^2}$. In the case of brachytherapy, Eq.

(6.11) and (6.13) substituted into Eq. (6.10) gives

$$\sigma_\alpha D_b = m(\bar{\alpha} D_b - \ln(k)) + n. \quad (6.15)$$

In the case of external beam therapy, a similar procedure gives

$$\sqrt{\sigma_\alpha^2 + d^2 \sigma_\beta^2} D_e = m([\bar{\alpha} + \bar{\beta} d] D_e - \ln(k)) + n. \quad (6.16)$$

Subtracting Eq. (6.16) from Eq. (6.15), and simplifying gives the final result

$$\frac{\bar{\alpha}}{\bar{\beta}} = \frac{d D_e}{(D_b - D_e) - \frac{1}{m} \frac{\sigma_\alpha}{\bar{\alpha}} \left(D_b - \sqrt{1 + d^2 \left(\frac{\sigma_\beta}{\sigma_\alpha} \right)^2} D_e \right)}. \quad (6.17)$$

6.5 Discussion

6.5.1 Possible bias of parameter estimates

A consequence of the results of this chapter is the possible existence of a bias on parameter estimates that is due to the dose range of the clinical data. If the slope of the linear correlation between $\overline{\alpha'}$ vs. $\ln(k)$ is inversely related to the dose of 50% tumour control, the obvious question to ask is whether there is a bias on parameter estimates obtained from a set of clinical data that does not include the dose of 50% tumour control. In other words, if the construction of a set of $\overline{\alpha'}$ and $\ln(k)$ parameter estimates produces a linear plot whose inverse slope is an estimate of the dose of 50% tumour control, will two competing sets of estimates, one obtained from a set of clinical data that includes the 50% response, the second set from clinical data (of the same disease) that does not include the 50% dose response, have the same slope, and hence have the same estimate of the dose of 50% tumour control? The methods and results of this chapter cannot answer this question. I suggest that this question is very important, and deserves future consideration. Brenner^{14,42} and others^{39,48,57,61,62} have assumed that unbiased radiobiological parameter estimates can be obtained by fitting a tumour control model to measured clinical data. However, it is not customary for clinically measured (and published) dose response data to include a 50% response, since dose escalation studies are usually performed on diseases with good prognostics. If the currently available clinical data were not suitable to obtain unbiased radiobiological parameter estimates, this would have broad implications for the practice of

radiobiological parameter estimation from clinical data.

Fig. 6.4 showed estimates for α/β plotted using Eq. (6.6), which uses estimates of the scaled parameter κ to obtain an α/β ratio as a function of $\ln(k)$. The estimates for α/β using Eq. (6.6) agrees very well with the results of Chapter 5, justifying its use. Eq. (6.6), however, used in concurrence with the principal result of this chapter (which is the interpretation of the D estimate that is obtained from the $\overline{\alpha'}$ vs. $\ln(k)$ parameter correlation as an estimate for the dose of 50% tumour control) allows additional physical insight that shows the potential problems in estimating α/β from clinical data. To illustrate this, Fig. 6.5 is a plot of the estimates of scaled parameters κ and D obtained from modelling of prostate cancer listed in Tables 6.1 and 6.2. In Fig. 6.5, the κ , D estimates have been converted into a coordinate on the TCP vs. dose space: since κ physically represents the logarithm of the remaining tumour cells, it was converted to a quantity that represents tumour control probability by taking its exponential twice, i.e. $TCP = \exp(-\exp(-\kappa))$. The quantity D has physical dimensions of dose, and so this value is plotted on the dose axis. Fig. 6.5 also includes the original clinical data reported by Stock, Pinover, and Hanks. The purpose of this figure is to show that the parameter D seems to correlate with the lowest dose point of the clinical data used in estimating the α and σ parameters for a given $\ln(k)$. For these data sets there is no measurement of the dose of 50% tumour control, so we cannot evaluate the accuracy of the estimates for it, however it is somewhat apparent from the lower two graphs of Fig. 6.5, obtained from the external beam dose escalation study, that the estimates for D

FIG. 6.5. Parameter estimates and clinical data for three clinically measured dose response studies for prostate cancer. Top: Low dose rate ^{125}I therapy of prostate cancer (Stock), middle and bottom: 2 Gy per fraction external beam therapy (Pinover and Hanks). The parameter estimates plotted here are derived from the linear relation of α and $\ln(k)$ parameters that are obtained when fitting a heterogeneous (population) and homogeneous (individual) tumour control model to clinical data. The numerical values are given in Tables 6.1 and 6.2.

seem to be at a dose that is credibly larger than what we would expect the 50% tumour control dose to be. In clinical experience, good results, implying significantly larger than 50% TCP, for early stage prostate cancer are usually associated with a dose of about 145 Gy for ^{125}I brachytherapy, and about 72 Gy for external beam teletherapy.⁵⁷ In Table 6.2, the rough value of 70 Gy is obtained as a dose estimate for both external beam therapies. This value of 70 Gy for external beam therapy is considerably higher than the 50% TCP dose that would be expected based on clinical experience, which supports the notion that there is a bias in these parameter estimates. Clearly this will translate into a bias in the final result of the α/β estimate, but it is difficult to quantify this without a better measurement of the true dose of 50% tumour control for external beam therapy, and a better understanding of the parameter bias due to the dose range of clinical data.

6.5.2 Link between isoeffect analysis and dose response modeling

The results of this chapter also help to unify TCP modelling of clinical data with the method of isoeffect analysis. Modelling TCP using clinical data can be understood using equations (6.6) and (6.7), which interpret the results of Chapter 5 in physical terms. These equations relate the α/β ratio to differential physical doses D_e and D_b , and a quantity that relates to tumour control, κ_e , and κ_b . When κ_e , and κ_b are the same, the external beam and brachytherapy dose response studies can be reduced to a single dose response at the same survival, which is the idea of isoeffect analysis. There is

consistency in the results of this section since Eqs. (6.6) and (6.7) reduce to Eq. (6.9) when κ_e and κ_b are equal. If κ_e does not equal κ_b , the survivals are not equal, and so Eqs. (6.6) and (6.7) suggest a correction to isoeffect analysis that depends on the absolute value of either $\bar{\alpha}$ or $\ln(k)$. However, (6.6) and (6.7) disagree with (6.9) since the results of the current chapter indicate that the value of D used in all these equations is in fact an estimate of the 50% TCP dose, which suggests that Eq. (6.9) is only valid at 50% tumour control dose. This interpretation of the results of Sections 6.2 and 6.3 are strengthened by Section 6.4, which shows that the value of the α/β ratio explicitly depends on heterogeneity and the survival level of the isoeffect used. At 50% tumour control, when m equals infinity, the effect of heterogeneity is nullified since the second term in the denominator in Eq. (6.17) goes to zero. At higher survival the amount of heterogeneity will always increase the α/β ratio since the effect of heterogeneity is to reduce the differential between low dose rate dose, and high dose rate dose, $D_b - D_e$. At lower than 50% survival, when m is negative, the effect of heterogeneity will be to decrease the α/β ratio due to the negative sign in the denominator of Eq. (6.17).

6.5.3 Confidence intervals

6.5.3.1 Dose escalation analysis

The large confidence intervals for α/β , shown in Fig. 5.5 and 6.4 may also be explained using the results of this chapter. If clinical data is only available at the high end of the tumour control spectrum, such as is the case with early stage prostate cancer,

it appears there is a difficulty in obtaining an accurate parameter estimate; this can be illustrated with the aid of Fig. 6.2(c) and (d). In constructing Fig. 6.2(d), linear regression was performed on each line of Fig. 6.2(c), in order to obtain each $\overline{\alpha'}$ and $\ln(k)$. Clearly, the greater the range of the data that make up each line in Fig. 6.2(c), the less uncertainty there is in the regression results, which are the slope and intercept; these are directly transformable into physical parameter estimates $\overline{\alpha'}$ and $\ln(k)$. This leads me to believe that the large confidence intervals for α/β given in Fig. 5.5(b) are due to the limited dose range of the data listed in Tables 5.1 to 5.3. To reduce these large confidence intervals on α/β , the results of this chapter indicate that data over as large a TCP range as possible is needed. Smaller error bars on each data point, which could be obtained by including larger numbers of patients in each dose response point, would also help reduce the confidence intervals. The results of this chapter suggest this would be of secondary importance to the survival range of data points.

6.5.3.2 Isoeffect analysis

The effect of heterogeneity on confidence intervals for prostate α/β determined by isoeffect analysis can also be investigated using Eq. (6.17). King used Eq. (6.9), and typical total dose values for ^{125}I low dose rate brachytherapy (145 Gy), and 2 Gy per fraction (typical total dose 72 Gy) to conclude that isoeffect analysis suggest a low α/β for prostate of about 2 Gy.⁵⁷ Table 6.3 was constructed using Eq. (6.17) with the same dose values used by King, and further assuming $\sigma_{\alpha}/\overline{\alpha}$ is 0.3, several values for $\sigma_{\beta}/\overline{\beta}$,

Table 6.3. Confidence intervals for individual α/β values (in Gy) as calculated using Eq. (6.17) and a Monte Carlo synthetic data method to generate the confidence intervals for individual α/β based on the population mean and variance of α and β . For all entries, $D_b = 145$ Gy, $D_e = 72$ Gy, $d = 2$ Gy, $TCP = 0.8$, $m = 1.2$, $\bar{\alpha} = 0.26$ Gy⁻¹, and $\sigma_{\alpha}/\bar{\alpha} = 0.3$.

	$\sigma_{\alpha}/\sigma_{\beta} = 2$	$\sigma_{\alpha}/\sigma_{\beta} = 2.39$	$\sigma_{\alpha}/\sigma_{\beta} = 5$	$\sigma_{\alpha}/\sigma_{\beta} = 10$	$\sigma_{\beta} = 0$
95% C.I. (L)	0.80	0.87	1.05	1.07	1.07
68.3% C.I. (L)	1.44	1.53	1.76	1.83	1.83
mean $(\bar{\alpha}/\bar{\beta})$	2.32	2.39	2.56	2.60	2.64
68.3% C.I. (H)	3.79	3.69	3.50	3.45	3.42
95% C.I. (H)	7.35	6.30	4.58	4.39	4.16
$\sigma_{\beta}/\bar{\beta}$	0.35	0.30	0.15	0.08	0.00

and using $\bar{\alpha} = 0.26$ [the mean value for α listed by Nahum²⁶]. Variation of $\bar{\alpha}$ from 0.05 to 0.5 Gy⁻¹ did not significantly affect the data in Table 6.3. Table 6.3 shows mean values and confidence intervals for $(\bar{\alpha}/\bar{\beta})$, which are the limits of the individual α/β values that would be expected in a heterogeneous population, as opposed to $\bar{\alpha}/\bar{\beta}$, which is the population mean of α divided by the population mean of β . Table 6.3 was constructed using a Monte Carlo synthetic data method where random values for α and β are generated according to Eq. (6.17).⁵³ Since it is assumed that α and β are not correlated, individual α/β can be determined by taking the ratio of randomly generated α and β ; the confidence interval for α/β is derived directly from the spectrum of ratios. Table 6.3 shows only the effect of heterogeneity in α and β on confidence intervals for $(\bar{\alpha}/\bar{\beta})$. It does not include uncertainty in the values of D_b and D_e , which occur due to uncertainties in dose delivery, such as set-up errors, organ motion or seed migration. A

full confidence interval for α/β should also include these uncertainties, and so the true confidence interval would be larger than what is shown in Table 6.3.

The values in Table 6.3 indicate a slight increase in the mean value of α/β when heterogeneity is considered, as compared to the homogeneous case, which predict α/β of about 2 Gy. The second column where $\sigma_\alpha/\sigma_\beta = 2.39$ is the case when $\sigma_\alpha/\sigma_\beta$ is also equal to $\overline{(\alpha/\beta)}$. The other columns investigate the effect of differing ratios of α to β variance. The principal result is that as the variance in β becomes more important, the wider is the confidence limit on individual α/β . This is expected since more variation in individual β implies some cases where an individual has high α and low β , or vice versa. The mean value of the population-averaged α/β varies only minimally with variance in β . Table 6.3 shows that consideration of heterogeneity in radiosensitivity alone (excluding heterogeneity in number of clonogens, or within the tumour) and ignoring uncertainties in the total doses, puts an upper confidence limit on α/β of about 7 Gy for high variance in β . Stated in another way, Table 6.3 says that if the variation in the β parameter is significant, one could expect about 2 to 3 patients per 100 to have an α/β for prostate above 7 Gy, and 1 in 6 to have α/β over 3.8 Gy, based on the usual doses used to treat ^{125}I brachytherapy and 2 Gy per fraction external beam therapy. Even for very low β heterogeneity, Table 6.3 indicates that about 1 in 6 patients would have α/β greater than 3.5 Gy if the coefficient of variation in α is 0.3.

Chapter 7

DISCUSSION

The previous two chapters are a discussion on the effect of population averaging of radiosensitivity in tumour control modeling. The principal conclusion is that the practice of parameter estimation from dose escalation data can do no better than estimate the dose of 50% tumour control (Section 6.2). The formulas obtained for α/β from dose escalation analysis, either in terms of $\ln(k)$, or α , Eqs. (6.6) and (6.7) reduce to the same formula as isoeffect analysis, Eq. (6.9) when the estimate for κ , the remaining number of clonogens after radiotherapy, are the same for two fractionation protocols. Combined with the result that the slope of α vs. $\ln(k)$ parameter estimates is

an estimate of the inverse of the 50% tumour control dose, this implies that the standard formula for α/β by isoeffect analysis is only valid when the effect is at 50%. This hypothesis is strengthened by heterogeneous isoeffect analysis, Eq. (6.17), which clearly shows that the standard formula for α/β by isoeffect analysis can only be applied when the total dose points are measured at 50% TCP.

The above result is important because it implies that a systematic error on parameter estimates may be caused by the dose range of the clinical data, and it also explains that reasonable confidence limits on parameter estimates can only be obtained by including measured outcome at survival that covers as large a TCP range as possible. The confidence limits for α/β that I obtained using the heterogeneous model were large because this data is collected at the high TCP portion of dose response. As illustrated by parameter scaling, the estimates for $\ln(k)$, which are obtained by finding the x -intercept of the linearized dose response plotted in the κ - A plane, will have large uncertainties if the linear extrapolation is done from a few points that are closely spaced at any region in the κ - A plot. Small confidence intervals can only be obtained using as much of the κ - A parameter space as is available, which translates into having dose response that was measured from as close to zero to as close to 100% TCP as possible. Obtaining such data is non-trivial since curable diseases that are treated in radiotherapy are only treated if good outcomes are possible. These are generally limited to early stage disease where it is assumed that local control determines the success of the therapy. Some advanced stage diseases are also treated in radiotherapy in order to

control symptoms. In these cases, the success rates are often lower. These results are not likely to be suitable for analysis by the present tumour control model since it is possible that local control may not determine the outcome; disease that is not included in the target tumour volume (due to spreading of the disease) may ultimately be responsible for failure of the therapy. In either case, results that cover a large portion of response, from 30% to 70% for instance, are not available. The only possibility of resolving this problem is to use a surrogate model, such as an animal model, or an *in vitro* model.

Section 6.2 is also important since it implies that in order to understand effects such as tumour growth^{48,62} and edema⁶¹ on parameter estimation, the principal difference these effects bring is the change in the dose of 50% tumour control for a given fraction dose. The importance of the results of Section 6.2 is also evident from the number of papers that have been published in the last year on parameter estimation from clinically measured data.^{60,63-66}

The goal of Chapters 5 and 6 was to investigate the use of clinically measured data to obtain an estimate for α/β for prostate, in the hopes of adding credibility to the hypothesis that large dose per fractions would be beneficial in the treatment of prostate cancer. There is an assumption that the linear quadratic model will describe cell survival equally well for large dose per fraction (Fowler has suggested as large as 10 Gy fraction doses^{45,46,67}) as well as small fraction dose. As discussed in the

introduction, the linear quadratic model of cell survival has been successfully applied in the radiotherapy clinic since the parameter ratio α/β has enabled a good understanding of fractionation. However, it has always been known that this model, while providing a good description of the initial part of the survival curve, fails to provide a good description at higher doses since the linear quadratic model predicts an ever increasing slope of cell survival, whereas a finite slope with mono-exponential behaviour is more often observed experimentally. When modelling clinical data using the linear quadratic model with the goal of establishing a basis for hypofractionation, the fundamental limits of the model must be understood.

A further need for investigating the high dose per fraction limit of the linear quadratic model has arisen from recent analysis of hypofractionated clinical data. A clinical dataset of early stage prostate cancer dose escalation that has not been discussed in this work is a series of high dose rate (HDR) brachytherapy boosts to external beam therapy published by Martinez.⁶⁸ This fractionation strategy is becoming increasingly popular; 10 patients have been treated using this protocol at the Ottawa Regional Cancer Centre in the past year. The fractionation protocol consists of external beam therapy given in 2 Gy fraction doses to a total of 46 Gy, followed by a boost dose consisting of either two or three high dose rate brachytherapy fractions. Martinez evaluated the benefit of dose escalation by recording the tumour control with 3 boost fractions of 5.5, 6, and 6.5 Gy, where 4-year survival was 0.45, 0.70 and 0.75. In the case of two fraction boosts, dose escalation was performed for fraction doses of 8.25,

8.75, and 9.5 Gy; tumour control was 0.87, 0.97 and 0.95 respectively at 4 years. The result, simply stated, was that Martinez observed a statistically significant increase in tumour control for the larger fraction doses, at approximately similar total dose. This observation is consistent with a low α/β ratio.

Two analyses of the Martinez HDR data have been performed and published, one by Brenner⁴² and a second by Wang.⁶² Brenner's analysis using the homogeneous model gave an α/β estimate of 1.2 Gy [0.03, 4.1] with $\alpha = 0.026 \text{ Gy}^{-1}$ and 138 clonogens. Wang's analysis is significantly different than Brenner's in that he obtained a best parameter estimate of $\alpha = 0$, $\beta = 0.044 \text{ Gy}^{-2}$, and 530 clonogens, giving an α/β ratio of 0. He did not investigate negative α since he considered these to be unphysical values, and so he limited his search to positive α . My own unpublished modelling for this data using the homogeneous model (the same as Brenner and Wang) yielded the parameter estimates of $\alpha = -0.11 \text{ Gy}^{-1}$, $\beta = 0.0283 \text{ Gy}^{-2}$, and 0.08 clonogens, which confirms that the data of Martinez is best represented by unphysical values of the linear quadratic parameters. Fixing α to be zero, and using the 3-year data that Brenner analysed, and applying the homogeneous model, I obtained a value of $\beta = 0.0257 \text{ Gy}^{-2}$, and 58 clonogens, which is close to Wang's result. Using the heterogeneous model, and limiting α and β to be positive, I obtained α and $\sigma_\alpha = 0$, $\beta = 0.049 \text{ Gy}^{-2}$, $\sigma_\beta = 0.01 \text{ Gy}^{-2}$, and 2280 clonogens.⁶⁹ The estimate of an unphysical (negative) value of α , implies that either the data suffer from some deficiency, (patient selection bias, poor

definition of outcome, inconsistent dosimetry or treatment technique) or the model is inappropriate, or both.

The clinical data used by Martinez does have some inconsistencies in it, which were discussed by Lee in a letter.⁷⁰ He observed that the Martinez' clinical data were not compiled in a randomized trial, and that according to an initial publication of Martinez, the eligibility criterion for entering the boost dose escalation study changed as the study progressed which resulted in patients with a more favourable prognosis being treated in the two boost fraction arm of the study. There is also an inconsistency in Brenner's analysis since Brenner used 3-year outcome (with one point from four year outcome) when 4-year outcome data were available to be analysed. Wang consistently used the 4-year data. The discussion of Lee is credible, and gives good reason to believe the data compiled by Martinez may be unsuitable for analysis with a tumour control model, and so unphysical parameter estimates may result. A detailed analysis would be required to determine which facets of the data are inconsistent, if it is even possible to definitely show inconsistencies in the data. Another possibility, however, is that the large fraction doses (especially the two fraction boosts, which were of 8.25 to 9.5 Gy) may be beyond the range where the linear quadratic model can reliably describe cell survival.

Another reason that modelling of large dose per fraction is needed comes from a little known fractionation protocol used in the UK between 1962 and 1984, where

prostate cancer was treated using 6 fractions of 6 Gy.⁷¹ This study reported results of 209 patients, whose initial stage was evaluated by transperineal biopsy and classified using the TNM (tumour-lymph node-metastases) system. Only patients with evidence of metastases were excluded; however, 129 of the 209 patients were classified as having late stage (T3 or T4). Assessment of lymph node involvement was not made. The results of this study are difficult to relate to the clinical data used in this thesis, since the results were compiled and published before the introduction of PSA. There is further complication since many patients in the study died of non-cancer causes, making it difficult to assess the outcome of the treatment. However, if the results of this protocol, which the authors characterize as ‘good’, are roughly considered to be equal to 2 Gy fractions given to a total dose of 76 Gy, which is typical of modern fractionation, then the α/β by isoeffect analysis, Eq. (6.8), is 1.6 Gy. The stability of this number is determined by considering different total doses to which the 6 Gy protocol is equivalent. If 36 Gy in 6 fractions is equal to 66 Gy in 2 Gy fractions, isoeffect gives an α/β ratio of 2.8 Gy. On the other extreme, if the equivalence is 84 Gy in 2 Gy fractions, then α/β equals 1 Gy. However, there exists a difficulty since in the same report, the authors report that a total of 55 Gy administered in 12 fractions (4.58 Gy/fraction) yields approximately equal results to the 36 Gy in 6 fractions. Applying Eq. (6.8) to the 36 and 55 Gy protocols then gives α/β of -1.9 Gy, which is not consistent with the formalism of the linear quadratic model. Again, the clinical data may be criticized since this last measurement is the result of only 20 patients.

The examples given here are not meant to prove an inconsistency in the linear quadratic model. This would require a much more detailed analysis. It is meant to support the view that to model hypofractionation, a requirement of a cell survival theory is that it should be stable to fraction doses of at least 10 Gy, if not larger. The following chapter examines the theoretical basis of the linear quadratic model with the purpose of evaluating the model's ability to characterize the high dose portion of the cell survival curve.

Chapter 8

FUNDAMENTAL LIMITS OF THE LINEAR QUADRATIC MODEL

In Chapter 2, the derivation of the linear quadratic model given by Chadwick and Leenhouts was summarized. The initial critique of the linear quadratic approach was that the final slope of cell survival was not constant; many cell survival curves exhibit a constant final slope. The linear quadratic approach survived, however, due to the correlation of α/β with clinically relevant effects, the so-called “early” and “late” effects. The poor description of the high dose region of cell survival by the linear quadratic has largely been forgotten. However, if clinical radiobiology is to be set on a solid foundation, it is imperative that all assumptions of the cell survival model be well known and open for debate. The purpose of this chapter is to illustrate a new method to

derive the linear quadratic cell survival equation, and to use it to explore the ability of the linear quadratic model to properly describe the large dose region of cell survival.

I will show that the linear quadratic formalism can only be derived by making a little known assumption regarding repair kinetics: that the reduction of sublethal lesions due to the consumption of these lesions during a lesion exchange process is small compared to the reduction of these lesions due to repair alone. This assumption was originally stated by Douglas Lea⁹ in 1946, and it has been discussed more recently,⁷²⁻⁷⁴ but the implications on the accuracy of the linear quadratic method at large dose per fraction have not been evaluated. Because of this assumption it is possible to model the repairable damage using a single parameter, namely β of the linear quadratic model. The consequence of this assumption is that repairable type damage increases without bound as dose increases, which in turn causes the ever increasing slope of the survival curve. Removal of this assumption produces a model that explicitly accounts for exchange as well as repair, and has the benefit of providing an upper bound on the steady-state quantity of repairable damage that can be produced in the cell. This translates into a single final slope of the cell survival curve. The initial description of the survival curve remains linear quadratic, since the relative importance of exchange vs. repair is only important at large doses.

The development of the linear quadratic model, and the development of the dose rate dependence were shown in Chapter 2. In that chapter, two methods were shown to

derive the G function, which is the dose rate modifying function of the linear quadratic model. In both methods used to derive the G function, the most important concept is that repair reduces the number of sublethal lesions. This is modeled using the function $\tau(t)$ in Eq. (2.16) and the term $-n/\tau$ in Eq. (2.19); both correspond to mono-exponential repair. It is important to recognize that using these two methods, there is an implicit assumption made about the relative importance of lesion reduction due to repair and exchange. Lea himself was aware of this assumption, which he stated: *“we can without great error make the simplifying assumption that the gradual diminution of free breaks which occurs after the cessation of radiation is solely due to restitution, and neglect the fact that exchange accounts for a small part of this diminution”*. (Page 263 of “Actions of Radiations on Living Cells”.⁹)

I have devised a representation of the linear quadratic model, shown in Fig. 8.1, which can be used to derive the full linear quadratic equation including the Lea-Catcheside dose protraction factor. Using this model it can be seen that the Lea-Catcheside factor can only be derived using an important assumption, which I restate: the reduction of sublethal lesions due to repair is large compared to the reduction due to the exchange of sublethal lesions. I consider this assumption to be a fundamental assumption of the linear quadratic model, and one that is not generally recognized. The first purpose of this chapter is to show that the compartmental model in Fig. 8.1 is a true representation of the linear quadratic model. This is accomplished by re-deriving the G function using the compartmental model in Fig. 8.1. To make the derivation

more accessible and to show that it is a true representation of the linear quadratic formalism, the derivation is compared line by line to a derivation by Dale⁷⁵. Dale's derivation is used since it is well known, and since the method can be further tested by also deriving the relative effectiveness (RE) function for the case of decaying sources, as Dale did. I suggest that a reproduction of Dale's derivation, which is the current standard of the linear quadratic formalism, is sufficient proof that the compartmental model shown in Fig. 8.1 is a true representation of the linear quadratic model with time dependence.

The second purpose of this chapter is to investigate the importance of Lea's assumption, that exchange of sub-lethal damage is much smaller than repair, on cell survival modeling and the possible effects relevant to the prostate α/β problem. This is done by deriving a modified linear quadratic cell survival equation in which Lea's assumption is removed. This modified linear quadratic model is shown in Fig. 8.2. Parameters are estimated for this new equation for some well-known cell survival lines: Hela⁷, Chinese Hamster,⁷⁶ and C3H,⁷⁷ and one cell line of clinical interest, human glioma cells.⁷⁸ To show that the modified linear quadratic model shown in Fig. 8.2 provides a superior representation of the final slope of the cell survival curve the following method is used. A set of parameter estimates is obtained for an entire set of cell survival points for both the linear quadratic and modified linear quadratic model.

FIG. 8.1. Compartmental model that is used to derive the linear quadratic formalism for cell survival including the Lea-Catcheside dose protraction factor. The symbols A, B and C are explained in Section 8.1.1.1.

FIG. 8.2. Compartmental model that considers simultaneous repair and exchange of sub-lethal damage.

New parameter estimates are then obtained by modeling a reduced portion of the measured dose response that omits the high dose region. This shows that the modified linear quadratic model provides a better description of the high dose region of dose response, and that the linear quadratic model provides a good description of the low dose region of cell response.

8.1 Derivation of linear quadratic and modified linear quadratic equations

8.1.1 Derivation of the G factor with comparison to Dale's 1985 method

8.1.1.1 Constant Dose Rate

The compartmental model under consideration is shown in Fig. 8.1. Three quantities, A, B and C are introduced: 'A' represents the number of potential target sites in a cell, 'B' is the number of sites within the cell where sub-lethal damage has been created and 'C' is the number of sites where irreparable damage exists. The production of 'B' lesions occurs at a rate of $2p$ multiplied by R , the dose rate. The constant ' p ' is defined in the same way as Dale¹² defines it. It is the yield per unit dose of sub-lethal lesions. The multiplier 2 is included because there are two potential target pairs required for sub-lethal lesions to interact. This is mainly a historical reason, used when sub-lethal lesions were considered to be single strand DNA breaks. It could be

omitted from this derivation; it is kept here to preserve the outcome of previous derivations. In Fig. 8.1, the number of sub-lethal lesions, B , is allowed to come to an equilibrium value before lesion interaction is considered. The sub-lethal lesions can repair with repair rate constant μ , so the number of repaired sites increases at the rate μB . The left of Fig. 8.1 can be used to write the differential equation for the number of sub-lethal lesions:

$$\frac{dB}{dt} = 2pR - \mu B \quad . \quad (8.1)$$

Eq. (8.1) is a restatement of Eq. (2.19). The solution is:

$$B(t) = \frac{2pR}{\mu} [1 - \exp(-\mu t)] \quad . \quad (8.2)$$

This is the second equation given in Appendix I of Dale.¹² The formation of irreparable lesions is considered next. This is accomplished by either of the two pathways shown on the right of Fig. 8.1. In the case of direct production of an irreparable lesion from a radiation event interacting with a site 'A', the model suggests that the production rate be proportional to the dose rate R , the proportionality constant being α . In the second pathway, the pre-existing sub-lethal lesions 'B' can interact with the formation of new 'B' lesions, the interaction probability being ϵ . New B lesions are produced at the rate pR , so the total rate of 'C' lesion production due to interaction of sub-lethal lesions is the product of the new lesion production rate, pR , with the number of pre-existing lesions, B , and the probability of interaction, ϵ . Thus, C lesions due to the B pathway are produced at the rate $pR\epsilon B$ where Eq. (8.2) is used to calculate B . The differential equation for 'C' can easily be written:

$$\frac{dC}{dt} = \alpha R + p R \varepsilon B . \quad (8.3)$$

Following Dale, the alpha-type damage occurs directly from 'A' to 'C', and the beta-type involves interaction through the B box. The equations are

$$\text{alpha-type} = \alpha R \int_0^T dt = \alpha RT, \quad (8.4)$$

$$\text{beta-type} = p R \varepsilon \int_0^T B(t) dt \quad (8.5)$$

$$= p R \varepsilon \int_0^T \frac{2pR}{\mu} [1 - \exp(-\mu t)] dt \quad (8.6)$$

$$= \frac{2\varepsilon p^2 R^2}{\mu} \left[T - \frac{1}{\mu} [1 - \exp(-\mu T)] \right]. \quad (8.7)$$

Replacing εp^2 with β and using the same expression for the relative effectiveness, RE , as did Dale: $RE = 1 + (\beta\text{-damage}) / (\alpha\text{-damage})$.

$$RE = 1 + \frac{\beta}{\alpha} \frac{2R}{\mu} \left[1 - \frac{1}{\mu T} [1 - \exp(-\mu T)] \right]. \quad (8.8)$$

The relative effectiveness is a dose rate figure of merit, showing how the biological effect differs from the effect of a low dose treatment, with only α -type cellular damage.

The formula for RE is derived from Eq. (2.22), where the multiplier of αD can be considered to be $[1 + (\beta\text{-damage}) / (\alpha\text{-damage})]$.

Eq. (8.6) is the seventh equation given in Appendix I of Dale, and Eq. (8.8) is the last equation in that Appendix. The only minor difference in this derivation is the omission of the term ' n ' used by Dale, representing the "number of target pairs". In this formulation this was not used since the box 'A' in Fig. 8.1 that represents Dale's ' n ' was explicitly introduced. The concept of 'A' is important since this is meant to represent the very much larger number of target pairs than the numbers B or C ever obtain. This is essential since it allows the parameters α and p to be considered constant and independent of B and C.

To obtain the formula for G , Eq. (8.7) can be simplified by making the same substitution, $\beta = \epsilon p^2$, factoring out T from the square brackets, multiplying by T/T , and substituting $D = RT$. This yields:

$$\text{beta-type} = \frac{2}{\mu T} \left[1 - \frac{1}{\mu T} [1 - \exp(-\mu T)] \right] \beta D^2 = G(\mu, T) \beta D^2. \quad (8.9)$$

Thus, Eq. (2.18) is derived using Fig. 8.1.

8.1.1.2 Decaying radioactive sources

In the case of treatment with radioactive sources which decay, such as ^{125}I implants for prostate brachytherapy, Eq. (8.1) becomes

$$\frac{dB}{dt} = 2 p R_0 e^{-\lambda t} - \mu B. \quad (8.10)$$

R_0 is the initial dose rate of the decaying source and λ is the decay constant. The solution is

$$B(t) = \frac{2pR_0}{\lambda - \mu} e^{-\mu t} \left[1 - e^{-(\lambda - \mu)t} \right], \quad (8.11)$$

which is equal to equation (iii) of Dale's Appendix II, where he treats decaying sources.

Eq. (8.3) becomes

$$\frac{dC}{dt} = \alpha R_0 e^{-\lambda t} + p R_0 e^{-\lambda t} \varepsilon B. \quad (8.12)$$

In keeping with the above definition of alpha and beta type damages, the alpha component of damage is the first term of Eq. (8.12) while the beta component is the second. Again, expressions for alpha and beta-type damages are obtained by substituting Eq. (8.11) into Eq. (8.12) and integrating. The result is

$$\text{beta-type} = p R_0 e^{-\lambda t} \varepsilon \int_0^T \frac{2pR_0 e^{-\mu t}}{\lambda - \mu} \left[1 - e^{-(\lambda - \mu)t} \right] dt, \quad (8.13)$$

$$\text{alpha-type} = \alpha R_0 \int_0^T e^{-\lambda t} dt. \quad (8.14)$$

Integrating Eq. (8.13) and substituting $\beta = \varepsilon p^2$ gives equation (iv) in Dale's Appendix II.

$$\text{beta-type} = \frac{2\beta R_0^2}{\mu - \lambda} \left[\frac{1}{2\lambda} \left[1 - e^{-2\lambda t} \right] - \frac{1}{\lambda + \mu} \left[1 - e^{-(\lambda + \mu)t} \right] \right]. \quad (8.15)$$

Integrating Eq. (8.14) gives equation (v) of Dale.

$$\text{alpha-type} = \frac{\alpha R_0}{\lambda} \left[1 - e^{-\lambda t} \right]. \quad (8.16)$$

The remainder of the derivation of the RE for decaying sources is equivalent to that of Dale, and his famous equation for the RE_∞ of decaying source treatments is equally obtained.

$$RE_\infty = 1 + \left(\frac{\beta}{\alpha} \right) \frac{R_0}{\mu + \lambda}. \quad (8.17)$$

8.1.2 A modified linear quadratic model that accounts for simultaneous exchange and repair of sublethal damage

Fig. 8.1 is peculiar since it treats the two processes yielding cell death independently in time, which is the effect of assuming that repair is the dominating process in determining the steady state value of B. The physical mechanism we wish to model is that repair and exchange act as simultaneous processes, which can be easily modeled using Fig. 8.2. I proceed by developing the equations for Fig. 8.2.

8.1.2.1 Constant dose rate

The differential equations that govern Fig. 8.2 are:

$$\frac{dB}{dt} = 2 p R - B (\mu + p R \varepsilon), \quad (8.18)$$

$$\frac{dC}{dt} = \alpha R + p R \varepsilon B. \quad (8.19)$$

Eq. (8.18) is similar to Eq. (8.1) except that there is an additional term $pR\epsilon$. As a first investigation into the behaviour of this system of equations, the variable $\mu' = \mu + pR\epsilon$ is introduced. This substitution makes Eq. (8.18) and Eq. (8.19) similar to Eq. (8.1) and (8.3). Using this, the expressions for RE and G are developed in a similar manner as Eq. (8.8) and (8.9). The results are

$$RE = 1 + \frac{\beta}{\alpha} \frac{2R}{\mu + pR\epsilon} \left(1 - \frac{1}{(\mu + pR\epsilon)T} (1 - \exp(-(\mu + pR\epsilon)T)) \right), \quad (8.20)$$

$$G'(\mu, p\epsilon, R, T) = \frac{2}{(\mu + pR\epsilon)T} \left(1 - \frac{1}{(\mu + pR\epsilon)T} (1 - \exp(-(\mu + pR\epsilon)T)) \right). \quad (8.21)$$

The prime notation is added to Eq. (8.21) to distinguish this G function from the original Lea-Catcheside function. Eq. (8.20) has a similar form to Dale's equation for RE , however there is an obvious difference since there is additional dose rate dependence rendering RE non-linear with dose rate, R , unlike Eq. (8.8). The G' function depends not only on T and μ , but also on the dose rate, R , as well as an additional parameter, $p\epsilon$.

8.1.2.2 Decaying dose rate

The differential equations in the case of decaying sources are

$$\frac{dB}{dt} = 2 p R_0 e^{-\lambda t} - B \left(\mu + p R_0 e^{-\lambda t} \varepsilon \right), \quad (8.22)$$

$$\frac{dC}{dt} = \alpha R_0 e^{-\lambda t} + p R_0 e^{-\lambda t} \varepsilon B. \quad (8.23)$$

Unlike the case of Fig. 8.1, where Eq. (8.17) gives the *RE*, these equations do not have a simple analytic solution. Since Eq. (8.17) is widely used, it is unfortunate that a comparable expression using Fig. 8.2 is not available. For dose rates normally used in permanent seed ^{125}I implants, numerical solution of Eq. (8.22) and (8.23) specifically for the decay of ^{125}I shows very little difference with Eq. (8.17), indicating that for low dose rates used clinically, the assumption that exchange is small compared to repair is valid.

8.1.2.3 Survival curve

The equation for the cell survival curve is derived by solving equations (8.18) and (8.19). The solution is

$$C(t) = \alpha R t + \frac{2 p^2 \varepsilon R^2}{\mu'} \left\{ t - \frac{1}{\mu'} [1 - \exp(-\mu' t)] \right\}, \quad (8.24)$$

where μ' replaces $\mu + p\varepsilon R$. Eq. (8.24) bears a similar resemblance to the traditional linear quadratic equation, which is given in Eq. (8.4) and (8.9). It approaches the linear quadratic equation at low dose, which can be seen by expanding the exponential

function in an infinite series and letting t tend to zero. However, Eq. (8.24) behaves quite differently from the linear quadratic model at large doses since this new formalism predicts a finite final slope. This is seen by differentiating Eq. (8.24) with respect to dose. For cell survival plotted on a semi-log plot, an expression for the logarithm of S is:

$$-\ln(S) = C(t) = \alpha R t + \frac{2\beta R^2}{\mu'} \left[t - \frac{1}{\mu'} [1 - \exp(-\mu' t)] \right]. \quad (8.25)$$

$p^2\epsilon$ was replaced with β . The final slope is obtained by differentiating with respect to dose.

$$\frac{d}{dD} \ln(S) = \frac{d}{dt} \frac{dt}{dD} \ln(S), \quad (8.26)$$

$$\frac{d}{dD} \ln(S) = \frac{d}{dt} \frac{1}{R} \ln(S), \quad (8.27)$$

$$-\frac{d}{dD} \ln(S) = \alpha + \frac{2\beta R}{\mu'} [1 - \exp(-\mu' t)]. \quad (8.28)$$

The final slope is obtained by evaluating at $t \gg \ln(2)/\mu'$.

$$-\left[\frac{d}{dD} \ln(S) \right]_{t \gg \frac{\ln 2}{\mu'}} = \alpha + \frac{2\beta R}{\mu'}. \quad (8.29)$$

This quantity is a constant value, which indicates a linear region of the survival curve at large dose.

8.2 Comparison of the linear quadratic and the modified linear quadratic model with experimental data

In fitting the modified linear quadratic model, Eq. (8.25), to cell survival data, the parameters ϵ , p and μ are correlated. In other words, one of these parameters must be known prior to fitting data to the cell survival data in order to determine all three of these parameters. This can easily be seen by inspection of Eq. (8.25). The numerator of the second term for $-\ln(S)$ has the quantity $p^2\epsilon$; the denominator consists of the quantity $\mu' = \mu + p\epsilon R$. Hence, it is only possible to determine the product $p\epsilon$, and not p and ϵ individually. The fitted value of μ is also affected since setting p fixes the product $p\epsilon$, due to the denominator of Eq. (8.25). Hence μ depends on p by the relation for μ' . It is possible to introduce suitable parameter scaling into Fig. 8.2 to remove this problem; however, certain extra measurements would have to be made in order to determine all parameters from fitting cell survival data to the models. It is beyond the goal of this work to consider this type of theoretical development, and so I proceed by fixing p to the value 1 Gy^{-1} for all modeling. This does not affect the fitted survival curve, nor does it affect the least squares statistic generated by the fits. It only affects the value of p relative to ϵ and μ . The value $p = 1 \text{ Gy}^{-1}$ is chosen to allow a simple comparison of the relative parameters μ and ϵ between different cell lines.

Fits of the linear quadratic model and the modified linear quadratic model, Eq. (8.25), are shown in Fig. 8.3, which shows cell radiation response for Hela cells,⁷

Chinese hamster cells,⁷⁶ human glioma cells,⁷⁸ and mouse embryo cells.⁷⁷ For each plot in Fig. 8.3 the dose response was fit to the linear quadratic, or modified linear quadratic models by minimizing the least squares function:

$$\chi^2 = \sum \frac{[\text{model} - \text{data}]^2}{\sigma_{\text{data}}^2}. \quad (8.30)$$

The term *model* is either the linear quadratic model, or the modified linear quadratic model, *data* is the measured dose response, and σ_{data}^2 is the variance of the measured dose response. The errors in measured data points are summarized in the caption of Fig. 8.3. For the modified model, the dose rate is needed for estimating parameters, and these are also listed in the caption of Fig. 8.3. The fitted parameters and the least squares statistic are listed on the inset of each graph.

To show that the modified linear quadratic model provides a statistically significant improvement in fits, the probability that the modified linear quadratic model would produce a least squares statistic equal to the statistic of the linear quadratic model was calculated. In the case of Hela cells, the least squares statistic for the linear quadratic fit to all points on the survival curve is 14.4, and the same statistic for the modified model is 7.4. Assuming the modified model follows a Chi-square distribution of 9 degrees of freedom (the number of data points less 4 modeled parameters less one) the probability of obtaining a least squares statistic of 14.4 or greater is approximately 10%. For the human glioma cells, this figure is about 5%, and for Chinese Hamster cells, this figure is less than 0.5%. The results for the mouse embryo cells are peculiar

since neither the linear quadratic nor the modified linear quadratic model provides a particularly good fit to the measured data. This is possibly due to the odd behaviour of the low portion of this survival curve, where some type of adaptive response⁷⁹ appears to be present. Nevertheless, visual inspection of the fits to the entire cell survival curve, as well as fits to a reduced portion of the survival curve show that the modified model provides a superior fit as compared to the linear quadratic model fit.

One of the early criticisms of the linear quadratic model was that it did not provide a good description of the high dose portion of the survival curve. The modified linear quadratic model, predicting a constant final slope, will improve this dose description. This is demonstrated by obtaining fits to cell dose response data that omit high dose points. These results are shown in Fig. 8.4 and Fig. 8.5. In Fig. 8.4, enough data points are included so that the modified linear quadratic model can properly estimate the final slope of the dose response. In this case, the modified linear quadratic model gives an acceptable representation (within experimental uncertainty) of high dose points, even though only 50% to 66% of the dose response is modeled. The linear quadratic model underestimates high dose survival by 66% for U87MG cells, to more than an order of magnitude for C3H cells. When modeling the very low dose portion of the survival curve the linear quadratic model provides an excellent fit to the very low portion of the dose response, as seen in Fig. 8.5. In contrast, the modified linear quadratic model has difficulty in this truly linear quadratic portion of dose response. In all four datasets presented here, the modified linear quadratic model produces an

FIG. 8.3. Cell survival fitting to several cell lines. Top left: HeLa cells. The dose rate used in the modeling was $R = 1.5$ Gy/min (dose rate of 100 to 200 rads/min is quoted in Puck). Uncertainties in the data are assumed to vary between 10% and 25%, as quoted in Puck. Top right: Chinese Hamster cells strain A. The dose rate quoted in Elkind is $R = 7.2$ Gy/min. Uncertainties in the data were assumed to be 10%. Bottom left: C3H cells, which are derived from mouse embryo cells. The dose rate quoted in Terzaghi is $R = 0.83$ Gy/min. Uncertainties in the data were estimated at 10% from error bars from survival curve. Bottom right: U87MG cells, which are derived from human glioma cells. $R = 1.6$ Gy/min (dose rate of 1.2 to 2.0 Gy/min is quoted in Heller). Uncertainties in the data vary between 10% and 25%, from error bars shown in Heller.

FIG. 8.4. Model fitting of measured cell survival of several cell lines with the high dose points removed. Top left: HeLa; top right: Chinese Hamster; bottom left: C3H, bottom right: U87MG. The purpose of this figure is to show that the modified linear quadratic model provides a better description of the high dose portion of cell response data. The closed points are points included in the fits, the open circles are measured data points, but not included in the fitting. In all cases, the modified linear quadratic model provides a better description of the high dose portion of the survival curve.

FIG. 8.5. Model fitting of measured cell survival of several cell lines using only the low dose portion. Top left: HeLa; top right: Chinese Hamster; bottom left: C3H, bottom right: U87MG. The purpose of this figure is to demonstrate that the LQ model provides a good description of the initial part of the cell survival curve. The closed points are points included in the fits, the open circles are measured data points, but not included in the fitting. The best-fit parameters for the modified linear quadratic model include unphysical values (negative values for μ). The reason is that the modified linear quadratic model predicts a constant final slope. Since the initial portion of the survival curve is truly linear quadratic, the best estimates for modified model are unphysical. This demonstrates the importance of having experimental data that properly describes the initial and final portion of the cell survival curve to obtain meaningful parameter estimates.

unrealistic value of the μ parameter when modeling only the low dose portion of the cell response data. The reason is that this portion of the cell response curve is truly linear quadratic. Since the modified linear quadratic model seeks to fit this to a curve with mono-exponential final slope, it must produce unphysical values of the μ parameter. However, it is clear from Fig. 8.3 that the modified linear quadratic model is capable of providing a good representation of the low dose portion of the survival, provided the data becomes linear at large doses. The purpose of this result is to emphasize that the linear quadratic model describes well the initial portion of the cell survival curve. This result is not obvious from Fig. 8.3, and so modeling of the low dose portion of the cell survival curve was included to demonstrate this.

8.3 Discussion

8.3.1 Link between modified linear quadratic and other models

To start the discussion, it should be emphasized that the modified model shown here is similar to the cybernetic and lethal-potentially lethal (LPL) models (Appendix A). The modified model closely resembles the cybernetic model; the reason is that both the linear quadratic and cybernetic models treat interaction of repairable damage in a similar manner. However, the linear quadratic model, as expressed by Chadwick and Leenhouts, deals with repair in a fundamentally different manner as the cybernetic model. The arguments given in this chapter show that assuming that a fixed proportion of sub-lethal damage is repaired results in the rate equations governed by Fig. 8.1. This

is equivalent to the assumption stated by Douglas Lea (that was reproduced in the introduction of this chapter); however it is difficult to appreciate the equivalence of these assumptions without Fig. 8.1. In the case of the cybernetic model, the fundamental difference between it and the modified linear quadratic model is the use of the sub-cellular view, and thus Poisson statistics. The cybernetic model, as it was originally stated could not have led to an understanding of fractionation effects as did the linear quadratic model; however, familiarity with the ideas of the cybernetic model led me to create Fig. 8.1 as the governing rate equations for the linear quadratic model.

In the case of the LPL model (Appendix A), the only difference with the modified linear quadratic model is the production rate of C lesions from interaction of B lesions. In the modified linear quadratic model, this term is $\rho \epsilon R B$, whereas in the LPL model, this term would be ϵB^2 . The difference is subtle, but significant. In the linear quadratic formalism, exchange is modeled by considering newly formed lesions interacting with pre-existing lesions. This has the effect that lethal lesions created via the interaction pathway can only be produced when the dose rate is non-zero, or in other words, when the radiation beam is on. This is somewhat troubling since some modern cell survival experiments are conducted at zero degrees Celsius, which is done precisely to remove the repair process and simulate high dose rate; hence the dynamics of the repairable pathway occur after irradiation is complete. The LPL model offers a slightly more physical interpretation by modeling interaction as being proportional to the concentration of sublethal lesions. Again, the purpose of this chapter is not to offer

a new model, or criticize a published model. It is simply to elucidate all the assumptions involved in the linear quadratic model so that these may be properly considered in evaluating the model.

8.3.2 Influence of constant final slope on α/β estimate

The difference in fitting behaviour between the modified linear quadratic and linear quadratic models can be described qualitatively: The linear quadratic model must play a game of compromise when fitting to experimental points that clearly show a constant final slope. In order to achieve a best fit the linear quadratic model tends to overestimate the initial slope of the survival curve and compensates at the high portion of the survival curve by underestimating β , in order to produce a survival curve that is essentially linear. This is seen in Fig. 8.3 where the linear quadratic best fits start with too steep a slope at low dose, then overestimates survival at the mid-dose range, and finally underestimates survival at the high dose range. This averaging of low and high dose response using the two-parameter fit is highlighted by providing fits to a reduced portion of the measured response. If the linear quadratic model were a true representation of the entire cell survival curve, estimated parameters, and the resulting fits, should be robust to the inclusion/exclusion of high dose points. The best fits plotted in Fig. 8.4 and Fig. 8.5 show that the linear quadratic model is sensitive to the modeled dose range, whereas the modified linear quadratic model is less sensitive to the dose range used in the modeling. This is attributable to the modified linear

quadratic model's better representation of the high dose portion of the cell survival curve. The implication is that for cell survival dose response curves with an evident final linear region, fitting of the data to the linear quadratic model will make α high and β low, and hence a higher α/β ratio. The consequences for cell survival modelling are important, and deserve consideration that is much broader than the scope of this chapter and of the entire investigation into prostate α/β .

8.3.3 Influence of the quality of cell survival data

The inspiration for this chapter was to investigate the effect of removing any assumption of the relative importance of sublethal damage interaction in the calculation of cell survival modeling. Section 8.3.2 indicates that when modelling cell survival curves that show a constant final slope, the linear quadratic model will compromise between low and high dose points to produce a best fit. For the cell types shown here, it appears that this effect becomes important at doses greater than about 4 to 6 Gy. However, this is clearly cell type dependent. In modeling of V79 cells⁸⁰ (which are a different type of Chinese hamster cells) whose results are not included here, no significant difference between the linear quadratic and the modified linear quadratic model were found for doses up to 12 Gy. It is also expected that many other cell lines will not exhibit any appreciable difference for best fits with the straight linear quadratic model and the modified linear quadratic model suggested here. For many published dose response data it was difficult to show the difference between the two versions of

the linear quadratic model since the data lacked the necessary quality; it was very important to use cell survival data that had a sufficient number of low dose points (i.e. less than 2 Gy) and high dose points (greater than 10 Gy). In cell survival datasets that lacked these points, either the modified linear quadratic model did not differ appreciably from the linear quadratic model, and gave negative μ values, (when high dose points were lacking) or the modified linear quadratic model gave unrealistic (negative) values for α when low dose points were lacking.

8.3.4 α/β for other cell survival models

The physical meaning of the α/β ratio, as it was defined in Section 2.2.1, is the dose where cell damage due to repairable lesions has equal importance as cell damage due to non-repairable lesions. The conclusion of Section 8.3.2 indicates that for cell lines that exhibit a constant final slope the α/β ratio may have conceptual problems due to the model's inability to describe properly the high dose region. Further, for the concept of α/β to produce consistent results in a macroscopic correspondence such as the correlation of the α/β ratio with the cell cycle, the ratio should be stable to the inclusion or exclusion of dose points. To take the example of the well-known HeLa cells, exclusion of high dose points leads to a credibly different estimate of α/β than that obtained by inclusion of all points. In Fig. 8.3, the linear quadratic fit to HeLa cells gives an α/β ratio of $(0.5371 \text{ Gy}^{-1})/(0.0681 \text{ Gy}^{-2})$, which equals 7.9 Gy. Excluding the 5 high dose points gives an α/β ratio of $(0.3488 \text{ Gy}^{-1})/(0.1284 \text{ Gy}^{-2})$, which equals 2.7

Gy, as shown in Fig. 8.5. This simple analysis does not include detailed statistics, so no formal conclusions can be drawn, however it is clear from a theoretical point of view that the linear quadratic model will not produce a stable α/β ratio with inclusion or exclusion of high dose points for cell lines that exhibit a constant final slope.

The modified linear quadratic model does not have a simple quantity that relates to the dose where repairable and non-repairable cellular damage are equally important in cell death; a similar exercise as in the preceding paragraph is not easily available. This does not exclude an α/β 'concept' from being applied to the modified linear quadratic model. It is a simple computational matter to calculate the dose where the 'alpha-type' and 'beta-type' damage pathways of Fig. 8.2 equally contribute to cell death. Further, this concept could be equally applied to most models that are discussed in Appendix A, notably the RMR and LPL models, or even the complicated Two-lesion kinetic model. I suggest that further development of these models in terms of some quantity regarding the ratio of repairable and non-repairable damage would be a good starting point in selecting a cell survival model which contains a quantity whose measurement is stable under dose range, which correlates to a macroscopic quantity such as the cell cycle, and which can characterize well the high dose portion of the cell survival curve.

Chapter 9

CONCLUSION

The effect of heterogeneity (variation of radiosensitivity amongst the population) on radiobiological parameter estimates obtained from modeling tumour control using clinically measured data has been investigated. It was found that the primary effect of heterogeneity was to increase the confidence intervals of the parameter estimates such that the statistical significance is considerably lower than is obtained using a homogeneous (individual) tumour control model. It was demonstrated that the population averaged tumour control model expressed in parameters of the linear quadratic model can be reformulated (scaled) in dimensionless parameters $\kappa = \alpha D - \ln(k)$, $A = \sigma D$, and $H = \sigma/\alpha$. In this formulation of the model, it has been shown that applying the heterogeneous (population) model to dose response data, the model produces an estimate of

the dose of 50% tumour control. A further result of the scaling theory is a correction term to the formula for α/β obtained from isoeffect analysis. The correction is due to heterogeneity, and vanishes when the isoeffect analysis is obtained at 50% tumour control. The fundamental limit of the α/β concept was investigated by demonstrating a new theoretical development of the linear quadratic expression. It was shown that cell survival can be expressed in terms of two variables (α and β) only if it is assumed that the reduction of sublethal lesions due their repair is large compared to the reduction due exchange. Removal of this assumption in the linear quadratic model produces a modified linear quadratic model that exhibits a constant final slope, which is consistent with experimental observations, as opposed to an ever-increasing slope that is predicted by the linear quadratic model.

Chapter 10

FUTURE WORK

In a study such as this one, where a relatively new idea is investigated, it often occurs that the study answers fewer questions than it poses. The conclusions stated in Chapter 7 are the hard conclusions that can be drawn from the arguments and discussions given in Chapters 5, 6, and 8. However, these conclusions lead to further questions about the use of tumour control models in measuring radiobiological parameters directly from measured clinical outcome. The principal questions can be separated into two groups: questions about tumour control modeling, and questions about cell survival modeling.

10.1 Tumour control model

The principal result of Chapter 6, which was stated in Section 6.2, is that the parameter correlation that exists between the radiosensitivity parameter and the logarithm of the number of tumour clonogens is an estimate of the dose of 50% tumour control. It is clear from Appendix C, and Section 5.1.1, that the same correlation would exist if the model were extended to include heterogeneity in $\ln(k)$ and tumour growth with the required modification to the σ^2 term, and the radiosensitivity term, α' . This correlation will also exist in the situation where the model is expanded to include intra-tumour heterogeneity. A non-uniform dose distribution can be reduced to a uniform dose distribution using the method of equivalent uniform dose.³ As explained in Appendix D, the most radioresistant cells within the tumour will dominate the tumour control for the individual, and so it is reasonable to consider the effective number of clonogens within the tumour to be the proportion of radioresistant clonogens that survive the radiosensitive clonogens. Hence, the results of Sections 6.2, 6.3 and 6.4 indicate that in order to determine the α/β ratio, it is necessary to determine the dose of 50% tumour control for two different dose-per-fraction protocols. This is quite a satisfying result other than the obvious ethical problem it poses of estimating the α/β ratio from human clinical data. The method of Chapters 5 and 6 shows this result to be derived directly from the Poisson model of tumour control, which was stated in Section 3.1.

To my knowledge, the idea that tumour control is achieved by removing all

clonogens, Eq. (3.3), has never been verified experimentally. There are a number of plausible alternatives to the idea that a single clonogen can repopulate a tumour. For instance, there may be some effect similar to the bystander effect, where tumour cells that are not irradiated self-induce death as a result of near neighbour sterilisation. Alternatively, there could be a minimum threshold of clonogens that need to be sterilized in order for the immune system to be able to remove a reduced number of tumour clonogens. Of a completely different idea, tumour control could be achieved not by removing tumour cells, but by targeting the tumour vasculature, inducing tumour death in a manner similar to the mechanisms hypothesised in angiogenesis.⁸¹⁻⁸⁶ This could be a real possibility if the tumour's blood vessel cells are more radiosensitive than the tumour cells. It is my opinion that, before altered fractionation protocols are developed, experimental scrutiny of the basic assumption is required.

The following type of experiments could test the single clonogen hypothesis. If the α/β ratio can be measured using Eq. (6.9), or (6.8) more generally, with the iso-response being 50% tumour control, then a series of measurements of the dose of 50% tumour control, with dose per fraction varying from low (low dose rate brachytherapy) to large, ($\sim 10 - 15$ Gy per fraction), should produce a result consistent with Eq. (6.8). The test of the single clonogen model comes from measuring response at different tumour sizes. As the tumour size increases, from small to large, more total dose is required to achieve 50% tumour control. The increase in total dose at different dose per fraction should be characterized by a stable ratio given by Eq. (6.8) for different tumour

sizes. Further, varying heterogeneity in radiosensitivity should not affect the stability of the total dose differential as long as it is measured at 50% TCP. These experiments would have to be done on an animal model since the requirement that the dose of 50% TCP be measured excludes the use of human data.

10.2 Cell survival characteristic relating to cell cycle

In a personal communication to me, Dr. Peter Raaphorst once noted an intriguing observation about the linear quadratic model. In general, when cell survival data is fitted to the linear quadratic model, if α is high often α/β is also high. Similarly, if α is low, then α/β is also often also low. The question he asked me was: is this a coincidence, is it a problem of mathematics, or is there a biophysical reason? In the case where the cell survival curve shows a constant final slope, Fig. 8.3, and the discussion in Section 8.3.2 suggest that Dr. Raaphorst's general observation may be due to limited ability of the linear quadratic model to describe the high dose region of cell survival. This leads me to speculate, along with the discussion relating the general observation of the link between cell cycle and α/β , that the effect of cell cycle on the survival curve is to increase the dose of the linear portion of the survival curve. In other words, cells that cycle quickly may have a survival curve that has a low dose shoulder, which quickly transitions to a linear region, whereas cells that cycle slowly have a broader shoulder, with a linear region that occurs at a dose that is often higher than the typical maximum dose values that are used to plot survival curves. The work

shown in Chapter 8 cannot prove this hypothesis. It is likely that cell survival data available in the literature would not be sufficient to model this since in many instances, either the low dose or high dose points that are needed to properly characterize the shoulder and linear region are omitted from the report. Investigation of this hypothesis would require many survival curve measurements that fully characterize the shouldered dose response in conjunction with accurate cell cycle measurements covering a large range of cell cycle times. As well, further theoretical work would be needed to define a quantity that would characterize the shoulder-linear transition position. These theoretical developments may involve further fine-tuning of the linear quadratic model, or perhaps the adoption of other cell survival concepts given in Appendix A.

Appendix A

ADDITIONAL CELL SURVIVAL MODELS

The purpose of this appendix is to summarize for completeness other published cell survival models that are not directly relevant to this thesis, but may be relevant to future cell survival model development aimed at generalizing or refining the α/β concept that was introduced in Section 2.2.1.

1. Target theory

A pioneer in radiation biology, Douglas Lea, proposed the target theory.⁹ In its simplest form, the expected number of biological lesions formed per cell is assumed to be proportional to the dose irradiated. In other words, the three terms in Eq. (2.1) are

assumed to be constant, and independent of dose. Lea wrote

$$S = e^{-\frac{D}{D_0}} = e^{-\lambda D}. \quad (\text{A.1})$$

The value D_0 is the dose required to reduce survival by a factor e , and λ is called the inactivation constant. Eq. (A.1) is known as single hit action. It is useful in describing radiation response to lower forms of cells such as bacteria. It is not applicable to many mammalian cell survival curves that exhibit a shouldered dose response as well as a constant final slope. The earliest form of a shouldered cell survival equation was obtained by considering a multi-target, single-hit mechanism. In this model, a cell was inactivated by single-hits of multiple targets within a cell. It is assumed that cell inactivation is created by several hits of different targets; all targets must be hit to create a lesion. It is required to inactivate n targets within a cell, where each target has equal inactivation constant λ . The probability of survival of the target (not hitting the target) is $e^{-\lambda D}$, and so the probability of hitting the target is $1 - e^{-\lambda D}$. Assuming each site is independent, the probability that all sites are hit is $(1 - e^{-\lambda D})^n$. This is also the probability that the cell is killed, so survival is given by

$$S = 1 - (1 - e^{-\lambda D})^n. \quad (\text{A.2})$$

At high doses Eq. (A.2) is approximated by:

$$S = ne^{-\lambda D} \quad (\text{A.3})$$

or,

$$\ln(S) = \ln(n) - \lambda D \quad (\text{A.4})$$

The final slope of the survival curve is constant and equal to $-\lambda$. The initial slope of Eq. (A.2) is given by evaluating dS/dD at D equal to 0.

$$\frac{dS}{dD} = n\lambda(1 - e^{-\lambda D})^{n-1} e^{-\lambda D}. \quad (\text{A.5})$$

The initial slope is equal to zero irrespective of n or λ . This property of the target theory is ultimately responsible for its eventual replacement by other models. The initial slope of cell survival is an important area of research today as many investigators have observed a fine structure experimentally, due to adaptive response⁷⁹. As well, it has been a tendency for some diseases to be treated by hyperfractionation, or small dose per fraction, in radiotherapy, necessitating a good description of the low dose region of the cell survival curve.

2. Repair saturation models

Thinking about cell survival models changed when it was recognised that cellular lesions were not static unlike the case for non-biologic material. In the early 1960's, the presence of a repair process was demonstrated by observing that the shoulder of a survival curve could be regenerated at high dose by irradiating the cell in two fractions.⁷⁶ By altering the time period between irradiations, the size of the second shoulder on the survival curve could be reduced to zero or reproduce the initial shoulder when the inter-dose period was varied from a long to short time. This result was interpreted as cellular damage being repaired between irradiations. With full repair between irradiations, the cells surviving the initial irradiation are returned to a normal

healthy state, and so the shoulder on the survival curve is repeated when the second irradiation is performed. Reduced repair is achieved by decreasing the inter-dose time. In this instance the repair is left partially complete, and so further irradiation is more effective in cell killing since biological defects remain from the initial exposure, and the second shoulder is less pronounced than the first.

In a saturable repair model, the mean number of lesions present in the cell is calculated by determining the equilibrium number of lesions present when lesions are created by the radiation exposure and then reduced by some repair mechanism. The shoulder on the survival curve is thought to be due to a reduced effectiveness of the repair mechanism. Two types of saturation have been suggested.^{87,88} The most common is the saturation of the repair system where the repair rate is limited by some bottleneck process, and thus saturates at large doses. Haynes⁸⁹, Calkins⁹⁰, and Sanches-Reyes⁹¹ have developed saturation models of this type. A second and distinct mechanism of saturation is one where the amount of repair diminishes with dose as the repair system becomes less able to repair lesions at high dose, which could be due to a lack of energy available to the repair system, or damage to the repair system by the radiation. This type of model was developed by Goodhead.⁸⁸

The idea of a saturable repair model was first discussed by Powers⁹², but never formulated into a mathematical model. Haynes⁸⁹ was the first to propose a formula for a survival curve based on a saturable repair mechanism and Eq. (2.3). Haynes reasoned

that the expected number of lesions per cell, and cell survival, at some time after irradiation should be:

$$-\ln(S) = (\text{number of lesions formed by radiation}) - (\text{number of repaired lesions})$$

or:

$$-\ln(S) = F(D) - R(D), \quad (\text{A.6})$$

where $F(D)$ is the lesion formation process and $R(D)$ is the removal of lesions by a repair process. Haynes assumed that the lesion formation process is proportional to the dose, such that $F(D) = \lambda D$, and that the repair process depends on limiting factors available to the cell. He suggested that the ability of the cell to repair lesions should saturate at a reasonably high dose, and further considered the formula $\alpha(1 - e^{-\beta D})$ to be a reasonably simple description of a limited repair ability of the cell. In this case, Eq. (A.6) becomes:

$$-\ln(S) = \lambda D - \alpha(1 - e^{-\beta D}). \quad (\text{A.7})$$

Eq. (A.7) has three variables instead of the two for the target theory, Eq. (A.2), but has several redeeming features that make it appealing.

The initial and final slopes of $\ln(S)$ in Eq. (A.7) are $-\lambda + \alpha\beta$ and $-\lambda$. They are both finite, and are realistic of most mammalian cell survival curves, unlike the zero initial slope of the multi-target, single-hit mechanism. As well, this model does not need to assume any type of lesion interaction, as does the multi-hit model. Further, the Haynes approach can be expanded to include physical interpretations of the parameters λ , α , and β ,⁹¹ which open the possibility of associating certain clinical effects with cell

survival parameters.⁹³

Subsequent to Haynes, Calkins further developed the repair saturation models by envisioning an enzymatic repair process.⁹⁰ He treated the repair process as having two distinct steps:

F and R and $\overline{FR}$ are the concentration lesions, repair enzymes, and the enzyme-lesion complexes; P is the concentration of repaired lesions; K_1 and K_2 are rate constants. Calkins treated this as a chemical kinetics problem and applied previously demonstrated results. He had to assume that the overall time of repair is the sum of the two steps, and he had to slightly manipulate published results since he was interested in the number of unrepaired lesions after the reaction was completed, and not the overall time of the reaction, as the rate kinetics problem was designed to determine. Using this method, Calkins obtained this formula for the number of unrepaired lesions:

$$R_0 t = -\frac{1}{K_1} \ln \frac{L}{L_0} + \frac{L_0}{K_2} \left(1 - \frac{L}{L_0} \right). \quad (\text{A.8})$$

In Eq. (A.8), R_0 is the initial number of repair enzymes per cell, and L_0 is the number of lesions formed from the irradiation. Calkins formulated a survival curve by solving Eq. (A.8) for L and applying this mean number of lesions to Eq. (2.3). Due to the manner the problem was formulated, the solution for L at infinite time is always zero since the solution for L in Eq. (A.8) exponentially tends towards zero. This led Calkins to introduce a then new idea into cell survival modeling. In order to obtain a finite number

of unrepaired lesions that contribute to cell death, Calkins introduced the idea that there is a maximum time for repair to take place; the damage becomes permanently fixed at a fixation time which is a property of the cell-irradiation system. He did not precisely define a mechanism for fixation, although he suggested the metabolism of DNA or protein synthesis. Fixation of radiation damage is an idea that is important today, and can be thought of as some type of chemical reaction with a biological lesion that renders the lesion non-repairable. Using Eq. (A.8), Eq. (2.3) and the idea of fixation, Calkins was able to generate a wide variety of cell survival shapes, with widely varying initial and final slopes as well as shoulder sizes.

Lastly, shouldered dose response curves were generated by Goodhead⁸⁸ using the concept of a limited pool of resources of the repair system. This paper was mostly phenomenological, and was meant to illustrate an alternative mechanism of shouldered dose response curves. He assumed that lesions are produced proportionally to the dose, and that lesions can be removed by a repair process at a rate proportional to the number of existing lesions (exponential repair). He further assumed that in the simplest case, the number of repair molecules is also reduced at a proportion of one to one to the numbers of repairs, and that the repair molecules are not replenished. He also applied the concept of a fixation time, as did Calkins. With this set of assumptions, and Eq. (2.3), Goodhead was also able to produce a series of survival curves that also are able to describe a wide variety of cell survival dose response, with varying initial and final slopes, and shoulder types.

Despite the relatively good description of cell survival by saturation models with few parameters and good physical interpretation, they have never been prevalent in either radiation biology or radiotherapy literature.

3. Lesion interaction models

A third class of cell survival models can be identified as distinct from both target theory and saturation repair models. These are known as lesion interaction models. The shouldered dose response is generated using the idea of two distinct types of lesions: lethal lesions that cannot be repaired, and sub-lethal lesions that can be repaired. Further, the sub-lethal lesions can be converted into a lethal lesion by interaction with a second sub-lethal lesion. The most famous of these models is the well-known linear quadratic model, but it is not the only model that has been applied to cell survival involving lesion interaction. Repair is also fundamental to lesion interaction models, but the repair is generally limited to constant repair ability; repair saturation is not considered.

3.1 Derivation of linear quadratic model due to Kellerer and Rossi

The linear quadratic model was independently derived by both Chadwick and Leenhouts and Kellerer and Rossi.⁸ The Chadwick and Leenhouts derivation was described in Section 2.1.1. Based on a series of experimental measurements of the radio-

biological effectiveness of neutrons, Kellerer and Rossi used the general observation that for a series of end-points, the radiobiological effectiveness, RBE, of neutrons is proportional to the inverse square of the neutron dose.⁸

$$\text{RBE} \propto (\text{neutron dose})^{-1/2} = \sqrt{\frac{\lambda}{D_n}}.$$

The RBE for neutrons is defined as the ratio of a neutron dose to a reference photon dose required to achieve an equivalent radiobiological effect (cell survival).

$$\text{RBE} = \frac{D_x}{D_n} = \sqrt{\frac{\lambda}{D_n}}. \quad (\text{A.9})$$

Thus, for an equivalent cell survival:

$$D_n = \frac{D_x^2}{\lambda}. \quad (\text{A.10})$$

The yield of biological lesions is normally considered to be proportional to the dose.

This is especially true for higher LET particles such as neutrons:

$$L = k_n D_n. \quad (\text{A.11})$$

Substituting Eq. (A.10) into Eq. (A.11) and letting $k = k_n/\lambda$, we obtain for photons:

$$L = k D_x^2. \quad (\text{A.12})$$

In essence, Equation (A.12) is a statement that in order for photons to create a lethal biological lesion (a lesion created by a neutron), the photon's lesions must interact. In this case, the general expression for the number of lesions produced by photon irradiation can be expanded from Eq. (A.12) to a general case:

$$L = k(\lambda D_x + D_x^2). \quad (\text{A.13})$$

In Eq. (A.13) the variable λ is included to also allow for the creation of lesions leading to a biological effect by a single photon event. Its value depends on the photon energy.

3.2 Cybernetic model

The cybernetic model was originally described by Kappos and Pohlit.⁹⁴ This model has almost never been used in analyzing cell survival curves, however it is an important model since many of its ideas have been retained in other models discussed further, and also because the cybernetic model closely parallels the linear quadratic model. The cybernetic model was the first paper that introduced the idea of dividing certain lesion categories into compartments, creating what has been called a ‘compartmental’ model. An illustration of this model is shown in Fig. A.1 (adapted from the original paper). This model proposes that the cell reaction to radiation be categorized into three states labeled A, B and C. In this illustration cells exist in state A which are unharmed or undamaged. State B represents damaged cells. The damage can be repaired, returning the cell to state A. In state C, however, cells have been damaged beyond repair and so cells reaching this state are doomed to die.

As a consequence of radiation, cells of state B or state C are produced at a rate proportional to the dose rate dD/dt and the number of cells in state A. The constants of proportionality are η_{AB} and η_{AC} . Repair of cells of state B is possible, and this is represented as a transition from state B to A with rate proportional to the number of cells in state B. The constant of proportionality is ϵ_{BA} . Cells in state B can also

FIG. A.1. Schematic diagram of the Cybernetic model. Adapted from Kappos, A. and Pohlit, W., "A cybernetic model for radiation reactions in living cells," *Int. J. Radiat. Biol.* **22**, 51-65 (1972).

transition to state C where damaged (but repairable) cells become unrepairable through an interaction with a pre-existing lesion. The transition rate is proportional to the number of cells in state B and the dose rate $\dot{D}$. With the aid of Fig. A.1, a series of differential equations that describe the process are written:

$$\frac{dN_A}{dt} = -\eta_{AB} \dot{D} N_A - \eta_{AC} \dot{D} N_A + \epsilon_{BA} N_B, \quad (\text{A.14})$$

$$\frac{dN_B}{dt} = \eta_{AB} \dot{D} N_A - \epsilon_{BA} N_B - \eta_{BC} \dot{D} N_B, \quad (\text{A.15})$$

$$\frac{dN_C}{dt} = \eta_{AC} \dot{D} N_A + \eta_{BC} \dot{D} N_B. \quad (\text{A.16})$$

Using Eq. (A.14), (A.15) and (A.16), an expression for the number of cells that have been lethally damaged, N_C , can be calculated. This model is different from the other models discussed in this appendix since the model considers damaged cells, as opposed to lesions within a cell. Hence survival is calculated by the quantity $N_A(D)/N_A(D=0)$, the number of cells in state A as a function of dose divided by the original number of cells. The assumption of Poisson statistics is not used.

The cybernetic model is similar to the linear quadratic model because it proposes three types of biological states of the cell: a healthy cell represented by state A in Fig. A.1; a cell that has been damaged, but the damage is repairable, state B; and unrepairable damage, where the cell's repair mechanism cannot repair the damage due to the ionizing radiation. A further similarity is the concept of lesion interaction, where a cell with two repairable lesions becomes a cell with a lethal lesion. This is shown in

Fig. A.1 with the pathway from state B to state C, and is represented mathematically in Eq. (A.15) and (A.16) with the introduction of the constant η_{BC} . The cybernetic model treats lesion repair in a more sophisticated manner than the linear quadratic model. In the Chadwick and Leenhouts formulation, the cell is considered to be able to repair a fixed proportion of repairable lesions. The numbers of single strand breaks in Eq. (2.6) and (2.7) are multiplied by a constant factor implying that a fixed proportion of repairable lesions are repaired. These terms were omitted from Eq. (2.12) since the constant proportionality factors do not alter the final form of the linear quadratic equation. The dose rate dependence in the linear quadratic model is achieved by calculating how the proportion of lesions that are repaired depends on the dose rate using either Eq. (2.15) or (2.19). The cybernetic model introduced a very important new concept to cell survival modelling in the manner it treats repair of sub-lethal lesions. Repair is treated using the pathway from state B to state A in Fig. A.1, which says that the repair rate is proportional to the number of cells in state B; repair is treated as mono-exponential. This method is distinctly different from the linear quadratic approach, which is to reduce by a fixed proportion the number of sub-lethal lesion exchanges that occur due to the mono-exponential repair of these lesions.

The fatal flaw of the cybernetic model is that it omits the consideration of multiple lesions within the cell. Since the model seeks to free itself of Eq. (2.3) it considers an extra-cellular view of cell survival, but in doing so it fails to account for the situation where the ionizing radiation has such linear energy transfer and fluence so

that we would expect multiple lesions (repairable and unrepairable) per cell. This consideration is central to Eq. (2.3) since we assume this multiple occurrence of lesions will have a specific form, that of a Poisson distribution.

3.3 The repair misrepair model

The repair misrepair model of cell survival of Tobias⁹⁵ advances cell survival modelling by incorporating biologic mechanism into the models. In previous models, repair was treated as a physical process with certain outcome. Lesions were repairable or not repairable; the models failed to consider the biologically reasonable situation where a lesion has been repaired but the repair was not successful. This is physically realistic, for instance, a cell can repair a double strand DNA break using the non-homologous repair mechanism, where the ends of the DNA molecule are simply re-joined by the repair enzymes without using a second strand as a repair template. If the lesion involves many base pairs, and the cell has no template to use to reconstruct the base pairs then it is entirely reasonable to assume that the repair process may have some flaws in it, and there may be alteration of the DNA sequence, forming a mutation that renders progeny non-viable. The essence of the repair-misrepair model is that it considers two types of repair: simple repair of a simple lesion, and complex repair of multiple lesions. In this model, each type of repair can be completed successfully, unsuccessfully, or not at all (fixation). The surviving fraction is obtained using Eq. (2.3), by assuming a Poisson distribution of lesions within the cell.

The model is shown graphically in Fig. A.2. Lesion formation is not separated into repairable and unrepairable, as they are in the linear quadratic or Cybernetic models. Tobias considers that when undamaged cells are exposed to ionizing radiation, lesions are produced at a rate proportional to the dose rate. At the instant of their creation, he refers to these lesions as uncommitted lesions. “Uncommitted” lesions are lesions whose endpoints have not been determined. The endpoint of a lesion can be successful repair to a healthy cellular state, incorrect repair to a non-healthy state, or no repair in which case there are remnant lesions at the time of fixation. This is a new idea of Tobias, the concept that not all attempts by the cell to repair itself lead to healthy cells. Hence, there is correct repair (denoted eurepair in the model) and incorrect misrepair.

In Fig. A.2, the number of lesions is given the symbol U , which stands for uncommitted. U is intended to represent the local concentration of uncommitted lesions, or the number of uncommitted lesions per cell. A differential equation for U can be written as:

$$\frac{dU}{dt} = \alpha \dot{D} - \lambda U - \kappa U^2 \quad (\text{A.17})$$

The number of lesions repaired linearly or quadratically can be determined by integrating $U(t)$:

$$U_l(t) = \int_0^t \lambda U dt \quad (\text{A.18})$$

FIG. A.2. Schematic diagram of the Repair-Misrepair Model. Adapted from Tobias, C.A., "The Repair-misrepair model in radiobiology: comparison to other models," *Radiat. Res.* **104**, S-77-S-95 (1985).

$$U_q(t) = \int_0^t \kappa U^2 dt \quad (\text{A.19})$$

The total number of lesions, $U_t(t)$ is the sum of un-repaired lesions, U , with linear and quadratic repaired lesions U_l and U_q :

$$U_t(t) = U(t) + U_l(t) + U_q(t) \quad (\text{A.20})$$

In order to calculate survival, the number of un-repaired lesions and misrepaired lesions are calculated using the probability of correct repair:

$$U_m(t) = U_t(t) - \phi U_l(t) - \delta U_q(t) \quad (\text{A.21})$$

U_m is intended to represent a mean number of the sum of un-repaired and misrepaired lesions per cell. The Poisson assumption is used in this model; the probability of survival is the probability of a cell having zero lesions given the expected mean number U_m . Using Eq. (2.3) the survival is written:

$$S = \exp(-U_m) \quad (\text{A.22})$$

The model can be adapted to many situations by assigning different lesion repair constants, λ and κ , and by allowing different repair fidelity constants, ϕ and δ . Tobias discusses one special case where all linear repair is eurepair and all quadratic repair is misrepair. This is equivalent to saying that $\phi = 1$ and $(1 - \delta) = 1$ or $\delta = 0$. In this case, Eq. (A.17) to (A.21) have an analytical solution, and survival can be given in terms of two variables, α and $\epsilon = \lambda/\kappa$.

$$S = e^{-\alpha D} \left\{ 1 + \frac{\alpha D}{\epsilon} \right\}^{\epsilon}. \quad (\text{A.23})$$

In the general case, both linear and quadratic repair can be successful or not, and so ϕ and δ can take on any value between zero and one: $0 \leq \phi \leq 1$ and $0 \leq \delta \leq 1$. To the author's knowledge, these cases have not been used at great extent in cell survival modeling other than a few exceptions.⁹⁶

3.4 Lethal and potentially lethal model

The lethal and potentially lethal (LPL) model of cell survival was introduced in 1985 by Curtis as a unified model.⁹⁷ Apart from the linear quadratic and target models, this is the only other model that has been used in the general literature to derive understanding of cellular response to radiation. In particular, it has been used in the study of dose rate effects; it is particularly well suited for this purpose. In a most general form, the LPL model is a combination of the cybernetic and repair-misrepair models. It is shown in Fig. A.3. In this model, the states B and C of the cybernetic model are preserved, however, the quantities B and C refer to the number of sublethal and lethal lesions within the cell, and not the number of cells that contain repairable or lethal lesions. Sublethal lesions are allowed to repair and interact, these two processes are limiting cases of the repair-misrepair model. Linear repair is considered to be always successful, and this is shown in the transition from the potentially lethal box to the undamaged cellular material box. It is considered to occur at a rate proportional to the number of sublethal lesions within the cell. Quadratic repair, or the interaction of

FIG. A.3. A schematic of the lethal potentially lethal model. Adapted from Curtis, S.B., "Lethal and potentially lethal lesions induced by radiation--a unified repair model," *Radiat. Res.* **106**, 252-270 (1986).

two lesions in a repair process is always considered to be unsuccessful, and this is shown in the transition from the repairable lesions to the lethal lesions box. Since this represents quadratic repair of the repair-misrepair model, the rate of transition to lethal lesions by the quadratic misrepair process is proportional to the concentration of lesions, the square of the number of sublethal lesions. This is consistent with the cybernetic model and linear quadratic model, which also allow transition to lethal lesion state by interaction of lesions, but is quite distinct in that this pathway is only supposed to represent lethal lesion formation by quadratic misrepair. In contrast, the cybernetic and linear quadratic models view this step as linear misrepair (in the terms of the repair-misrepair model).

3.5 Two-lesion kinetic model

The last model to be discussed is the two-lesion kinetic model of Stewart.⁹⁸ This is a relatively new model, published in 2001, and continues the evolution of the cybernetic, repair-misrepair, and lethal-potentially lethal models. A schematic representation is shown in Fig. A.4. The inspiration for this model is clearly to provide a theoretical foundation for the measurement of double strand breaks, and chromosome aberrations. A new feature of this model is the distinction of two types of lesions, simple lesions and complex lesions. Simple lesions have fewer than a cut-off number of base-pair damage. Stewart suggests 10 to 20 base pairs as a reasonable cut off point. The reasoning for dividing lesions into two categories is that multi-exponential repair has been observed experimentally. Deviation from mono-exponential repair can

be explained by second order repair kinetics of the repair-misrepair model, or by a saturated repair mechanism, or by two distinct repair pathways, as the two lesion kinetic model suggests. For simple and complex lesions, the model suggests different rates of formation and linear repair. As in the repair misrepair model, linear repair can either be performed correctly or incorrectly. Like the lethal-potentially lethal model, all quadratic repair is never performed correctly. Further, simple and complex lesions can interact, and be repaired quadratically; this repair is also never correct. Both simple and complex lesions can be permanently fixed. The model extends beyond lesion formation and considers the realistic case where a genetic defect may or may not have an effect on the genomic stability of the cell. In other words, not all permanent DNA lesions lead to a chromosome aberration and cell death. Fixed lesions always lead to cell death, but linear and quadratic repairs of both simple and complex lesions can either lead to a lethal or non-lethal genetic alteration.

This model is not simply a cell survival model; it is designed for use in conjunction with measurements of cell survival and DNA double strand break formation. This is also a new feature of this model, as it is the first to suggest that a simple cell survival curve may not be sufficient to determine all parameters in the model. It has a large number of parameters: α , p , λ_1 , λ_2 , η_1 , η_2 , η_{12} , α_1 , α_2 , β_1 , β_2 , γ_1 , γ_2 , γ_{12} . It has been evaluated and compared to the linear quadratic model by Guerrero,⁹⁹ who showed that the linear quadratic model, with two repair terms, is a good approximation of the two-lesion kinetic model.

FIG. A.4. A schematic representation of the two-lesion kinetic model.

Appendix B

THE LYMAN NORMAL TISSUE COMPLICATION MODEL

The approach to normal tissue complication probability (NTCP) estimation that is most often used in the clinic is based on a phenomenological approach that has been developed by Lyman.^{1,2} This approach relies on the general observation that for an organ that is partially irradiated, the probability of complication increases in a sigmoid fashion from zero at low dose and low volume to one at sufficiently large dose and volume. The sigmoid shape can be well described by the cumulative distribution of a Gaussian function. With suitable parameters in the Gaussian function, the complication function can be fit to clinically observed complications probabilities. The first part of the method to estimate complication probability is to construct a two-dimensional complication function that varies between zero and one as a function of the dose administered to a fraction of the tumour volume. Using a Gaussian distribution, the

complication function used by Lyman is

$$C(D, V) = C(\tau) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\tau} e^{-t^2/2} dt, \quad (\text{B.1})$$

where τ is given by

$$\tau = \frac{D - TD_{50/5}(v)}{mTD_{50/5}(v)}. \quad (\text{B.2})$$

The value $TD_{50/5}(v)$ is the tolerance dose for 50% complications after 5 years, and v is a partial volume of the organ, $v = V/V_{ref}$. The tolerance dose of the partial volume of the organ is related to the tolerance dose of the entire organ by a power law:

$$TD(v) = \frac{TD(1)}{v^n}, \quad (\text{B.3})$$

where $TD(1)$ is the tolerance dose of a uniformly irradiated organ. The parameters m , n , and $TD(1)_{50/5}$ fully characterize Eq. (B.1). They can be obtained by fitting this equation to clinical data. A clinically relevant dataset that Eq. (B.1) can be fit to was compiled by Emami;¹⁰⁰ fitted parameters n , m , and $TD(1)_{50/5}$ for this dataset were estimated by Burman.¹⁰¹

The second part of the method to estimate complication probability involves obtaining an appropriate dose that would be applied to a partial volume of the organ that would yield equivalent complications as the planned dose distribution. The NTCP is then calculated by using this dose-volume coordinate in Eq. (B.1). This is non-trivial since the dose distribution to the normal tissue is in general quite inhomogeneous, and there is really no universally accepted manner of reducing a

complex dose distribution to a uniform dose irradiating a partial volume which results in equal complications. This is also an assumption of the method: all dose distributions can be reduced to a single homogeneous dose that irradiates a partial volume of the organ at risk; the partial and uniform irradiation will yield equivalent complications to the original dose distribution. There have been empirical dose-volume histograms reduction algorithms (recipes) that have been published,^{2,102} and Niemierko¹⁰³ has shown that these do have some biological basis. A physical approach has been employed by Mohan,¹⁰⁴ who observed that if the assumption that NTCP can be invariant is true, the derivative of Eq. (B.1) with respect to τ should be zero. Mohan thus obtained a formula for dose reduction,

$$D_{\text{eff}} = \left[\sum_i \Delta V_i (D_i)^{1/n} \right]^n. \quad (\text{B.4})$$

The summation is over small volume elements, ΔV_i , of the organ at risk.

The phenomenological method of Lyman is appealing since there is reasonable confidence that the calculated NTCP will reflect the true complication probability that is likely to occur, because this method is in essence an interpolation of clinically measured results. It suffers because it relies heavily on sparse clinical data, and the only well-used data compilation, Emami,¹⁰⁰ includes only a few complication data points. There have been some attempts to construct a more biologically based method to estimate normal tissue complications.¹⁰⁵⁻¹⁰⁷ In order to model normal tissue complications using a “first principles” model, it is necessary to employ some fundamental

model of the organ at risk. In the instance of the tumour, the model that is employed is that all tumour clonogens must be sterilised. In the case of normal tissue, the situation is more complicated since the reduction of cells has different effects on different organs. For instance, for some patients, the surgical removal of a portion of a lung yields only a marginally reduced pulmonary capacity. In contrast, damage to a small portion of the spinal cord can result in permanent paralysis of one or several limbs. Evidently, different models are needed to describe the radiation damage complication probability of the spinal cord and the lungs. To address this, two different models to normal tissue have been suggested: the critical volume model,^{103,106} and the parallel architecture model.^{105,107} In the critical volume model, it is hypothesised that an organ consists of a group of elements required for its function; failure of any of the elements results in failure of the entire organ. A physical analogy is often made to a series electrical circuit where failure of any element in the circuit results in failure of the entire circuit. To model an organ more like the lungs, a “parallel” architecture model has been proposed where, like in the electric circuit analogy, failure of a single element reduces the capacity of the organ, but there exists a threshold number of elements that must fail in order for the organ to fail. Development of these models utilises the binomial approach where the organ is viewed as a collection of sub-units, each of which can remain viable or fail as a result of the exposure. In the critical volume model, failure of a single element results in a complication, and so the mathematical formulation of the model is the expression for zero occurrences of a sub-unit failure. The parallel architecture model is an extension of this concept, except that the probability that n or more occurrences of a sub-unit failure is required for organ failure.

Appendix C

REDUCTION OF A DOUBLE INTEGRAL FOR TUMOUR CONTROL OVER α AND β TO A SINGLE INTEGRATION OVER A COMBINED VARIABLE $\alpha + \beta d$

The purpose of this appendix is to show that the population averaged tumour control model, where the averaging is done over the α and β variables

$$TCP = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \frac{\exp\left(-\frac{1}{2} \left[\frac{(a - \bar{\alpha})^2}{\sigma_{\alpha}^2} + \frac{(b - \bar{\beta})^2}{\sigma_{\beta}^2} \right] - k e^{-(a+b)d} D\right)}{2\pi\sigma_{\alpha}\sigma_{\beta}} da db, \quad (C.1)$$

is equivalent to a population averaged model where the averaging is done over a combined radiosensitivity variable $\bar{\alpha}'$, given by $(\bar{\alpha} + \bar{\beta} d)$, in the special instance where the dose per fraction, d , is constant and the variance of the combined variable $(\bar{\alpha} + \bar{\beta} d)$ is taken as the variance of α and β added in quadrature, $\sigma_{(\alpha + \beta d)}^2 = (\sigma_{\alpha}^2 + d^2 \sigma_{\beta}^2)$.

The proof begins by applying a change of variable to Eq. (C.1):

$$x = a + bd, \quad (C.2)$$

$$y = b. \quad (C.3)$$

Using these transformations, the area element $dadb$ expressed in the x - y coordinate system is $dxdy$. This can be seen using a relation due to Jacobi.

$$\iint f(a,b) dadb = \iint f(\phi(x,y), \phi(x,y)) D(x,y) dxdy, \quad (C.4)$$

where $a = \phi(x, y)$ and $b = \phi(x, y)$ and

$$D(x, y) = \begin{vmatrix} \frac{\partial \phi}{\partial x} & \frac{\partial \phi}{\partial y} \\ \frac{\partial \phi}{\partial x} & \frac{\partial \phi}{\partial y} \end{vmatrix}. \quad (C.5)$$

Using the variable transformations of equations (C.2) and (C.3) gives $a = x-yd$ and $b = y$. Taking the partial derivatives, and substituting these in to Eq. (C.5) gives $D(x, y) =$

1. Eq. (C.1) written in terms of x and y is:

$$TCP = \frac{1}{2\pi \sigma_\alpha \sigma_\beta} \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \exp \left\{ -\frac{1}{2} \left[\frac{(x-yd-\bar{\alpha})^2}{\sigma_\alpha^2} + \frac{(y-\bar{\beta})^2}{\sigma_\beta^2} \right] - ke^{-xD} \right\} dydx. \quad (C.6)$$

The tumour control model, $\exp(-ke^{-xD})$, can be taken out of the y -integration as it does not depend on y . The expression within the square brackets can be expanded to:

$$\left[\frac{(x-yd-\bar{\alpha})^2}{\sigma_\alpha^2} + \frac{(y-\bar{\beta})^2}{\sigma_\beta^2} \right] = \left\{ \frac{(x-\bar{\alpha})^2}{\sigma_\alpha^2} + \frac{\bar{\beta}^2}{\sigma_\beta^2} \right\} + y^2 \left\{ \frac{1}{\sigma_\beta^2} + \frac{d^2}{\sigma_\alpha^2} \right\} - 2y \left\{ \frac{d(x-\bar{\alpha})}{\sigma_\alpha^2} + \frac{\bar{\beta}}{\sigma_\beta^2} \right\}. \quad (C.7)$$

Completing the square on the terms with y^2 and y gives

$$\begin{aligned}
y^2 \left\{ \frac{1}{\sigma_\beta^2} + \frac{d^2}{\sigma_\alpha^2} \right\} - 2y \left\{ \frac{d(x-\bar{\alpha})}{\sigma_\alpha^2} + \frac{\bar{\beta}}{\sigma_\beta^2} \right\} = \\
\left\{ y \left[\frac{\sqrt{\sigma_\alpha^2 + d^2 \sigma_\beta^2}}{\sigma_\alpha \sigma_\beta} \right] + \left[\frac{d(x-\alpha)}{\sigma_\alpha^2} + \frac{\beta}{\sigma_\beta^2} \right] \left[\frac{\sigma_\alpha \sigma_\beta}{\sqrt{\sigma_\alpha^2 + d^2 \sigma_\beta^2}} \right] \right\}^2 - \\
\left[\frac{d(x-\alpha)}{\sigma_\alpha^2} + \frac{\beta}{\sigma_\beta^2} \right]^2 \left[\frac{\sigma_\alpha^2 \sigma_\beta^2}{\sigma_\alpha^2 + d^2 \sigma_\beta^2} \right]. \tag{C.8}
\end{aligned}$$

Expression (C.8) consists of a squared term and a second term, which is a function of x only. Like the tumour control expression, the part of (C.8) which has no y -dependence can be moved outside the y -integration. The y -integration now takes the form of a Gaussian integral:

$$\int_{-\infty}^{\infty} \exp[-(\zeta y + \mu)^2] dy,$$

where ζ is the variance, and μ , the mean value. Integrating over all space, the value of the Gaussian integral only depends on the variance, not the mean, hence the y -integration will only depend on the modifier of y in (C.8). Performing the y -integration gives:

$$y\text{-integral} = \sqrt{2\pi} \left(\frac{\sigma_\alpha \sigma_\beta}{\sqrt{\sigma_\alpha^2 + d^2 \sigma_\beta^2}} \right). \tag{C.9}$$

The integral from (C.6) now reduces to the value of the y -integral (C.9) multiplied by the remaining x -integration from (C.7) and (C.8),

$$\frac{1}{2\pi\sigma_\alpha\sigma_\beta}\sqrt{2\pi}\left(\frac{\sigma_\alpha\sigma_\beta}{\sqrt{\sigma_\alpha^2+d^2\sigma_\beta^2}}\right)$$

$$\int_{-\infty}^{\infty}\exp\left\{-\frac{1}{2}\left[\frac{(x-\alpha)^2}{\sigma_\alpha^2}+\frac{\beta^2}{\sigma_\beta^2}-\left(\frac{d(x-\alpha)}{\sigma_\alpha^2}+\frac{\beta}{\sigma_\beta^2}\right)^2\frac{\sigma_\alpha^2\sigma_\beta^2}{\sigma_\alpha^2+d^2\sigma_\beta^2}\right]-ke^{-xD}\right\}dx.$$

(C.10)

With some manipulation, the term in the square brackets reduces,

$$\frac{(x-\bar{\alpha})^2}{\sigma_\alpha^2}+\frac{\beta^2}{\sigma_\beta^2}-\left(\frac{d(x-\bar{\alpha})}{\sigma_\alpha^2}+\frac{\bar{\beta}}{\sigma_\beta^2}\right)^2\frac{\sigma_\alpha^2\sigma_\beta^2}{\sigma_\alpha^2+d^2\sigma_\beta^2}=\frac{[x-(\bar{\alpha}+\bar{\beta}d)]^2}{\sigma_\alpha^2+d^2\sigma_\beta^2}.$$

(C.11)

Canceling terms in (C.10) and substituting (C.11) gives the final result,

$$\frac{1}{\sqrt{2\pi}\sqrt{\sigma_\alpha^2+d^2\sigma_\beta^2}}\int_{-\infty}^{\infty}\exp\left\{-\frac{1}{2}\left[\frac{[x-(\bar{\alpha}+\bar{\beta}d)]^2}{\sigma_\alpha^2+d^2\sigma_\beta^2}\right]-ke^{-xD}\right\}dx.$$

(C.12)

Expression (C.12) shows that using the variables $\bar{\alpha}'=(\bar{\alpha}+\bar{\beta}d)$, and $\sigma^2=(\sigma_\alpha^2+d^2\sigma_\beta^2)$ (C.1) can be written:

$$\frac{1}{2\pi\sigma_a\sigma_b}\int_{-\infty}^{\infty}\int_{-\infty}^{\infty}\exp\left\{-\frac{1}{2}\left[\frac{(a-\bar{\alpha})^2}{\sigma_\alpha^2}+\frac{(b-\bar{\beta})^2}{\sigma_\beta^2}\right]-ke^{-(a+b)D}\right\}da\,db=$$

$$\frac{1}{\sqrt{2\pi}\sigma}\int_{-\infty}^{\infty}\exp\left\{-\frac{1}{2}\left[\frac{[x-\bar{\alpha}']^2}{\sigma^2}\right]-ke^{-xD}\right\}dx.$$

Appendix D

A MONTE CARLO BASED TUMOUR CONTROL MODEL

Tumour control models require three things to be modeled: the spatial and temporal radiosensitivity of the tumour stem cells; the dose-time relationship of the tumour cells; and the probability that no stem cells remain given the expected number of survivors. Several assumptions are made to keep the model practical:

It is assumed that the tumour dose is spatially uniform and constant throughout radiotherapy. This is a first order approximation that may be acceptable for external beam radiotherapy, where uniform dose to the tumour and constant dose per fraction are goals of the therapy, but clearly incorrect for other types of therapies such as brachytherapy where the dose is known to be spatially inhomogeneous.

It is assumed that the linear quadratic model of cell survival adequately predicts survival with only the α and β parameters. Based upon some experimental observations,³⁰ it is assumed that α and β parameters are normally distributed within the population of patients.

No variation of cellular radiosensitivity within the tumour (no intra-tumour variation of radiosensitivity) was assumed. It is difficult to assess the degree of intra-tumour variation of radiosensitivity due to hypoxia, cell cycle redistribution, or simply due to a subpopulation of resistant or sensitive cells.²² It may be important to consider these cells since the most radioresistant cells within the tumour can dominate the TCP expression.²⁹ These populations may be the appropriate tumour sub-group that should be modeled if they are more radioresistant than the bulk of the tumour depending on the relative size and radiosensitivity of the sub-group. The assumption of no intra-tumour radiosensitivity is meant to apply to the sub-population of the most radioresistant stem cells within the tumour.

Normally, tumour growth is considered to be exponential. In this work prostate cancer was modeled, which is known to be slowly growing (estimated to have a cell doubling time on the order of 34 days or more¹⁰⁸), thus tumour growth was ignored. The Poisson model was used to relate the number of expected survivors to clinical

outcome.

For the present work it is assumed that the number of tumour clonogens is uniform in the population. It is normally assumed that the log of the number of tumour clonogens, $\ln(k)$, is Gaussian distributed, or k is log-normally distributed, and the method below can easily accommodate this. Roberts²³ showed that for $\ln(k)$ less than an order or 12, 10^5 cells, the variation in α dominates the population tumour control model. The goal of this work, however, is to investigate variation of radiosensitivity in a population, and so variation in $\ln(k)$ is not considered.

The procedure is as follows:

1. The inputs into the method are the linear quadratic parameters α , β and $\ln(k)$, their standard errors (σ_α^2 , σ_β^2), the total dose D , and the dose per fraction d .
2. Determine the linear quadratic parameters for an individual (α_i , β_i and $\ln(k)_i$) by generating a Gaussian distributed random number about the given mean and standard error. In the case of $\ln(k)$, $\sigma_{\ln(k)}^2$ is taken to be zero, so $\ln(k)_i$ equals $\ln(k)$.
3. For each individual i , calculate the surviving number of stem cells, k using the linear quadratic model: $k_{si} = \exp\{-\alpha D - \beta d D + \ln(k)\}$.
4. Generate a Poisson distributed random number about k_{si} . If this number is zero,

increase a counter N_{cured} by one. N_{cured} represents the number of patients whose tumours are controlled.

5. Repeat steps 2 to 4 N_{patient} times.
6. The tumour control probability is $N_{\text{cured}}/N_{\text{patient}}$.

This method is similar to the model published by Webb²⁴ with the exception that the β parameter is treated separately from the α parameter. A fixed α/β ratio was not used, as Webb assumed. This model is equivalent to the double integral,

$$\frac{1}{2\pi\sigma_a\sigma_b} \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \exp\left(-\frac{1}{2}\left[\frac{(a-\bar{\alpha})^2}{\sigma_a^2} + \frac{(b-\bar{\beta})^2}{\sigma_b^2}\right] - k e^{-(a+b)D}\right) da db.$$

Appendix E

CONFIDENCE INTERVALS FOR α/β AND OTHER PARAMETERS

This appendix describes the Monte Carlo method that was used to estimate the confidence intervals in the estimates for α , α' , H, and α/β for the fits to Stock, Pinover and Hanks dose response data in Chapters 5 and 6. The procedure was derived from a method described by Press.⁵³

1. For each clinical dose response point in Stock, Pinover and Hanks, calculate the uncertainty assuming the distribution is a binomial distribution. $\sigma_{bNEDi} =$

$$\frac{\sqrt{N_i P_i (1 - P_i)}}{N_i}, \text{ where } N_i \text{ is the number of patients in the data point, and } P_i \text{ is}$$

the $bNED = n_i/N_i$ where n are the number of successes and N is the number of trials.

2. Generate simulated dose response points by generating one random number, n_{gen} , distributed by a binomial distribution of n_i successes in N_i trials for each dose response point of Stock, Pinover and Hanks. The simulated data point, $bNED_i$, equals n_{gen}/N_i and the standard deviation is the value calculated in step one.

3. Determine best-fit parameters α_j and σ_j for each of the Stock, Pinover and

Hanks data by minimizing the function $\sum_i \frac{(TCP - bNED_i)^2}{\sigma_{bNEDi}^2}$ where TCP is the

heterogeneous or homogeneous tumour control model. Repeat this at fixed $\ln(k) = 0, 2.3, 4.6, \dots, 23$. This gives 10 α_j and σ_j for each of Stock, Pinover and Hanks. (In other words, reproduce Fig. 5.2, but with no error bars.)

4. For each $\ln(k)$ of Stock, Pinover and Hanks, calculate $H_j = \sigma_j/\alpha_j$. By comparing

α_j and α_j' directly, calculate $(\alpha/\beta)_{S,j} = \frac{d\alpha}{\alpha' - \alpha}$ (Eq. 5.5) for Pinover and Hanks.

As well, for all data points for each of Stock, Pinover and Hanks calculate the slope and intercept of α vs. $\ln(k)$. From the slope and intercept, calculate κ_j and

D_j for each of Stock, Pinover and Hanks, and then calculate $(\alpha/\beta)_{M,j}$ for each $\ln(k)$ using Eq. (6.6) also for Pinover and Hanks.

5. Repeat steps 2-4 many times (in this case 5000) and generate distributions for α , σ , χ^2 , $(\alpha/\beta)_S$, $(\alpha/\beta)_M$ for each value of $\ln(k) = 2.3, 4.6, \dots, 23$. Also generate distributions of κ_j , D_j . Only one κ_j and D_j is generated at each step 4.

Determine the mean and 95% confidence interval for all quantities in step 5 directly from their distributions by finding the cutoff value of the lowest 2.5% and highest 2.5% of the values in the distributions determined from step 5.

References

1. J. T. Lyman, "Complication probability as assessed from dose-volume histograms," *Rad. Res.* **104**, S-13-S-19 (1985).
2. J. T. Lyman and A. B. Wolbarst, "Optimization of Radiation Therapy, III: A method of assessing complication probabilities from dose-volume histograms," *Int. J. Radiat. Oncol. Biol. Phys.* **13**, 103-109 (1987).
3. A. Niemierko, "Reporting and analyzing dose distributions: A concept of equivalent uniform dose," *Med. Phys.* **24**, 103-110 (1997).
4. E. J. Hall, "Radiobiology for the Radiologist," Fifth Edition, Lippincott Williams & Wilkins, Philadelphia (2000).
5. K. H. Chadwick and H. P. Leenhouts, "A molecular theory of cell survival," *Phys. Med. Biol.* **18**, 78-87 (1973).

6. M. N. Cornforth and J. S. Bedford, "A quantitative comparison of potentially lethal damage repair and the rejoining of interphase chromosome breaks in low passage normal human fibroblasts," *Radiat. Res.* **111**, 385-405 (1987).
7. T. T. Puck and P. I. Marcus, "Action of x-rays on mammalian cells," *J. Exp. Med.* **103**, 653-666 (1956).
8. A. M. Kellerer and H. H. Rossi, "The Theory of Dual Radiation Action," *Current Topics in Radiation Research Quarterly* **8**, 85-158 (1972).
9. D. E. Lea, "Actions of Radiations on Living Cells," University Press, Cambridge (1946).
10. D. J. Brenner, Y. Huang, and E. J. Hall, "Fractionated high dose-rate versus low dose-rate regimens for intracavitary brachytherapy of the cervix: equivalent regimens for combined brachytherapy and external irradiation," *Int. J. Radiat. Oncol. Biol. Phys.* **21**, 1415-1423 (1991).
11. K. H. Chadwick and H. P. Leenhouts, "The Molecular Theory of Radiation Biology," Springer-Verlag (1981).
12. R. G. Dale, "The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy," *Br. J. Radiol.* **58**, 515-528 (1985).
13. M. C. Carlone, D. E. Wilkins, B. Nyiri, and G. P. Raaphorst, "Clinical radiobiology, early and late responding tissues, and hypofractionation for prostate cancer," *InterACTIONS* **49**, 14-20 (2003).
14. D. J. Brenner and E. J. Hall, "Fractionation and protraction for radiotherapy of prostate carcinoma," *Int. J. Radiat. Oncol. Biol. Phys.* **43**, 1095-1101 (1999).
15. H. R. Withers, "Biologic basis for altered fractionation schemes," *Cancer* **55**, 2086-2095 (1985).
16. J. F. Fowler, "The linear-quadratic formula and progress in fractionated radiotherapy," *Br. J. Radiol.* **62**, 679-694 (1989).

17. G. W. Barendsen, "Dose fractionation, dose rate and iso-effect relationships for normal tissue responses," *Int. J. Radiat. Oncol. Biol. Phys.* **8**, 1981-1997 (1982).
18. J. Denekamp, "Tumour stem cells: facts, interpretation and consequences," *Radiother. Oncol.* **30**, 6-10 (1994).
19. T. R. Munro and C. W. Gilbert, "The relation between tumor lethal doses and the radiosensitivity of tumour cells," *Br. J. Radiol.* **34**, 246-251 (1961).
20. J. D. Fenwick, "Predicting the radiation control probability of heterogeneous tumour ensembles: data analysis and parameter estimation using a closed-form expression," *Phys. Med. Biol.* **43**, 2159-2178 (1998).
21. G. K. Zagars, T. E. Schultheiss, and L. J. Peters, "Inter-Tumor heterogeneity and radiation dose-control curves," *Radiother. Oncol.* **8**, 353-362 (1987).
22. A. Niemierko and M. Goitein, "Implementation of a model for estimating tumor control probability for an inhomogeneously irradiated tumor," *Radiother. Oncol.* **29**, 140-147 (1993).
23. S. A. Roberts and J. H. Hendry, "A realistic closed-form radiobiological model of clinical tumor-control data incorporating intertumor heterogeneity," *Int. J. Radiat. Oncol. Biol. Phys.* **41**, 689-699 (1998).
24. S. Webb and A. E. Nahum, "A model for calculating tumour control probability in radiotherapy including the effects of inhomogeneous distributions of dose and clonogenic cell density," *Phys. Med. Biol.* **38**, 653-666 (1993).
25. P. E. Lindsay, V. V. Moiseenko, J. Van Dyk, and J. J. Battista, "The influence of brachytherapy dose heterogeneity on estimates of alpha/beta for prostate cancer," *Phys. Med. Biol.* **48**, 507-522 (2003).
26. A. E. Nahum, B. Movsas, E. M. Horwitz, C. C. Stobbe, and J. D. Chapman, "Incorporating clinical measurements of hypoxia into tumor local control modeling of prostate cancer: implications for the alpha/beta ratio," *Int. J. Radiat. Oncol. Biol. Phys.* **57**, 391-401 (2003).

27. S. L. Tucker, H. D. Thames, and J. M. Taylor, "How well is the probability of tumor cure after fractionated irradiation described by Poisson statistics?" *Radiat. Res.* **124**, 273-282 (1990).
28. S. L. Tucker and J. M. Taylor, "Improved models of tumour cure," *Int. J. Radiat. Biol.* **70**, 539-553 (1996).
29. M. Zaider and G. N. Minerbo, "Tumour control probability: a formulation applicable to any temporal protocol of dose delivery," *Phys. Med. Biol.* **45**, 279-293 (2000).
30. F. M. Buffa, S. E. Davidson, R. D. Hunter, A. E. Nahum, and C. M. West, "Incorporating biologic measurements (SF(2), CFE) into a tumor control probability model increases their prognostic significance: a study in cervical carcinoma treated with radiation therapy," *Int. J. Radiat. Oncol. Biol. Phys.* **50**, 1113-1122 (2001).
31. O. Algan, C. C. Stobbe, A. M. Helt, G. E. Hanks, and J. D. Chapman, "Radiation inactivation of human prostate cancer cells: the role of apoptosis," *Radiat. Res.* **146**, 267-275 (1996).
32. T. L. DeWeese, J. M. Shipman, L. E. Dillehay, and W. G. Nelson, "Sensitivity of human prostatic carcinoma cell lines to low dose rate radiation exposure," *J. Urol.* **159**, 591-598 (1998).
33. J. T. Leith, L. Quaranto, G. Padfield, S. Michelson, and A. Hercbergs, "Radiobiological studies of PC-3 and DU-145 human prostate cancer cells: x-ray sensitivity in vitro and hypoxic fractions of xenografted tumors in vivo," *Int. J. Radiat. Oncol. Biol. Phys.* **25**, 283-287 (1993).
34. R. G. Stock, N. N. Stone, A. Tabert, C. Iannuzzi, and J. K. DeWyngaert, "A dose-response study for I-125 prostate implants," *Int. J. Radiat. Oncol. Biol. Phys.* **41**, 101-108 (1998).
35. G. E. Hanks, T. E. Schultheiss, A. L. Hanlon, M. Hunt, W. R. Lee, B. E. Epstein, and L. R. Coia, "Optimization of conformal radiation treatment of prostate cancer: report of a dose escalation study," *Int. J. Radiat. Oncol. Biol. Phys.* **37**, 543-550 (1997).

36. W. H. Pinover, A. L. Hanlon, E. M. Horwitz, and G. E. Hanks, "Defining the appropriate radiation dose for pretreatment PSA $\leq$ 10 ng/mL prostate cancer," *Int. J. Radiat. Oncol. Biol. Phys.* **47**, 649-654 (2000).
37. D.E. Wilkins, J.E. Cygler, G. Perry, M.C. Carlone, and G.P. Raaphorst, "Radiobiological considerations in fractionation of radiotherapy for prostate cancer," *Proceedings of the Canadian Organization of Medical Physics 47th Annual Scientific Meeting*, 15-17 (2001).
38. C. R. King and C. S. Mayo, "Is the prostate alpha/beta ratio of 1.5 from Brenner & Hall a modeling artifact," *Int. J. Radiat. Oncol. Biol. Phys.* **47**, 536-539 (2000).
39. J. Fowler, R. Chappell, and M. Ritter, "Is alpha/beta for prostate tumors really low?" *Int. J. Radiat. Oncol. Biol. Phys.* **50**, 1021-1031 (2001).
40. C. S. Wu and M. Zaider, "A calculation of the relative biological effectiveness of ^{125}I and ^{103}Pd brachytherapy sources using the concept of proximity function," *Med. Phys.* **25**, 2186-2189 (1998).
41. R. Taschereau, R. Roy, and J. Pouliot, "Relative biological effectiveness enhancement of a ^{125}I brachytherapy seed with characteristic x rays from its constitutive materials," *Med. Phys.* **29**, 1397-1402 (2002).
42. D. J. Brenner, A. A. Martinez, G. K. Edmundson, C. Mitchell, H. D. Thames, and E. P. Armour, "Direct evidence that prostate tumors show high sensitivity to fractionation (low alpha/beta ratio), similar to late-responding normal tissue," *Int. J. Radiat. Oncol. Biol. Phys.* **52**, 6-13 (2002).
43. J. P. Logue, R. A. Cowan, and J. H. Hendry, "Hypofractionation for prostate cancer," *Int. J. Radiat. Oncol. Biol. Phys.* **49**, 1522-1523 (2001).
44. R. G. Dale and B. Jones, "Is the alpha/beta for prostate tumors really low? In regard to Fowler et al., *IJROBP* 2001;50:1021-1031," *Int. J. Radiat. Oncol. Biol. Phys.* **52**, 1427-1428 (2002).
45. J. F. Fowler, R. J. Chappell, and M. A. Ritter, "The prospects for new treatments for prostate cancer," *Int. J. Radiat. Oncol. Biol. Phys.* **52**, 3-5 (2002).

46. J. Fowler, M. Ritter, R. Chappell, and D. J. Brenner, "What hypofractionated protocols should be tested for prostate cancer," *Int. J. Radiat. Oncol. Biol. Phys.* **56**, 1093-1104 (2003).
47. W. D. D'Souza and H. D. Thames, "Is the alpha/beta ratio for prostate cancer low?" *Int. J. Radiat. Oncol. Biol. Phys.* **51**, 1-3 (2001).
48. J. Z. Wang, M. Guerrero, and X. A. Li, "How low is the alpha/beta ratio for prostate cancer?" *Int. J. Radiat. Oncol. Biol. Phys.* **55**, 194-203 (2003).
49. M. C. Carlone, D. Wilkins, B. Nyiri, and G. P. Raaphorst, "Comparison of alpha/beta estimates from homogeneous (individual) and heterogeneous (population) tumor control models for early stage prostate cancer," *Med. Phys.* **30**, 2832-2848 (2003).
50. S. Levegrun, A. Jackson, M. J. Zelefsky, M. W. Skwarchuk, E. S. Venkatraman, W. Schlegel, Z. Fuks, S. A. Leibel, and C. C. Ling, "Fitting tumor control probability models to biopsy outcome after three-dimensional conformal radiation therapy of prostate cancer: pitfalls in deducing radiobiologic parameters for tumors from clinical data," *Int. J. Radiat. Oncol. Biol. Phys.* **51**, 1064-1080 (2001).
51. S. Webb, "Optimum parameters in a model for tumor control probability including interpatient heterogeneity," *Phys. Med. Biol.* **39**, 1895-1914 (1994).
52. "Consensus statement: guidelines for PSA following radiation therapy. American Society for Therapeutic Radiology and Oncology Consensus Panel," *Int. J. Radiat. Oncol. Biol. Phys.* **37**, 1035-1041 (1997).
53. W. H. Press, B. P. Flannery, S. A. Teukolsky, and W. T. Vetterling, "Numerical Recipes in C," Cambridge (1988).
54. G. Cowan, "Statistical Data Analysis," Clarendon Press, Oxford (1998).
55. B. M. Dubray and H. D. Thames, "The clinical significance of ratios of radiobiological parameters," *Int. J. Radiat. Oncol. Biol. Phys.* **35**, 1099-1111 (1996).

56. D. J. Brenner, "Toward optimal external-beam fractionation for prostate cancer," *Int. J. Radiat. Oncol. Biol. Phys.* **48**, 315-316 (2000).
57. C. R. King and J. F. Fowler, "A simple analytic derivation suggests that prostate cancer alpha/beta ratio is low," *Int. J. Radiat. Oncol. Biol. Phys.* **51**, 213-214 (2001).
58. D.J. Brenner and E.J. Hall, "Low alpha/beta values for prostate cancer appear to be independent of modeling details," *Int. J. Radiat. Oncol. Biol. Phys.* **47**, 538-539 (2000).
59. M. C. Carlone, D. Wilkins, B. Nyiri, and G. P. Raaphorst, "TCP isoeffect analysis using a heterogeneous distribution of radiosensitivity," *Med. Phys.* **31**, In press (2004).
60. P. Stravec, B. Warkentin, N. Stavreva, and G. Fallone, "Evaluation of a closed-form tumor-control probability solution," *Med. Phys.* **29**, 1294-1294 (2002).
61. H. B. Kal and M. P. R. Van Gellekom, "How low is the alpha/beta ratio for prostate cancer," *Int. J. Radiat. Oncol. Biol. Phys.* **57**, 1116-1121 (2003).
62. J. Z. Wang, X. A. Li, C. X. Yu, and J. DiBiase, "The low alpha/beta ratio for prostate cancer: What does the clinical outcome of HDR brachytherapy tell us?" *Int. J. Radiat. Oncol. Biol. Phys.* **57**, 1101-1108 (2003).
63. A. Dasu, I. Toma-Dasu, and J. F. Fowler, "Should single or distributed parameters be used to explain the steepness of tumour control probability curves?" *Phys. Med. Biol.* **48**, 387-397 (2003).
64. M. Guerrero and X. Allen Li, "Analysis of a large number of clinical studies for breast cancer radiotherapy: estimation of radiobiological parameters for treatment planning," *Phys. Med. Biol.* **48**, 3307-3326 (2003).
65. N. Stavreva, P. Stavrev, B. Warkentin, and B. G. Fallone, "Derivation of the expression for $\gamma(50)$ and $D(50)$ for different individual TCP and NTCP models," *Phys. Med. Biol.* **47**, 3591-3604 (2002).

66. P. van Luijk, T. C. Delvigne, and J. M. Schippers, "Estimation of parameters of dose-volume models and their confidence limits," *Phys. Med. Biol.* **48**, 1863-1884 (2003).
67. J. Fowler, "Failla Lecture, Research in Radiation Biology and Physics," Forty Ninth Annual Meeting of the Radiation Research Society 2002
68. A. A. Martinez, L. L. Kestin, J. S. Stromberg, J. A. Gonzalez, M. Wallace, G. S. Gustafson, G. K. Edmundson, W. Spencer, and F. A. Vicini, "Interim report of image-guided conformal high-dose-rate brachytherapy for patients with unfavorable prostate cancer: the William Beaumont phase II dose-escalating trial," *Int. J. Radiat. Oncol. Biol. Phys.* **47**, 343-352 (2000).
69. M.C. Carlone, D. Wilkins, and G.P. Raaphorst, "Radiobiological parameter estimation for a predictive tumour control model for early stage prostate carcinoma," *Polish J. Med. Phys. & Eng.* **9**, 931-945 (2003).
70. W. R. Lee, "In regard to Brenner et al., *IJROBP* 2002;52:6-13," *Int. J. Radiat. Oncol. Biol. Phys.* **53**, 1392- (2002).
71. R. W. Lloyd-Davies, C. D. Collins, and A. V. Swan, "Carcinoma of prostate treated by radical external beam radiotherapy using hypofractionation. Twenty-two years' experience (1962-1984)," *Urology* **36**, 107-111 (1990).
72. D.J. Brenner, L.R. Hlatky, P.J. Hahnfeldt, Y. Huang, and R.K. Sachs, "The linear-quadratic model and most other common radiobiological models result in similar predictions of time dose relationships," *Radiat. Res.* **150**, 83-91 (1998).
73. R.K. Sachs, P.J. Hahnfeldt, and D.J. Brenner, "The link between low-LET dose-response relationships and the underlying kinetics of damage production/repair/misrepair," *Int. J. Radiat. Biol.* **72**, 351-374 (1997).
74. R.K. Sachs, A.M. Chen, and D.J. Brenner, "Proximity effects in the production of chromosome aberrations by ionizing radiation," *Int. J. Radiat. Biol.* **71**, 1-19 (1997).
75. P. R. Bevington, "Data Reduction and Error Analysis for the Physical Sciences," McGraw-Hill (1969).

76. M. M. Elkind and H. Sutton, "Radiation Response of Mammalian Cells Grown in Culture. 1. Repair of X-Ray Damage in Surviving Chinese Hamster Cells," *Radiat. Res.* **13**, 556-593 (1960).
77. M. Terzaghi and J. B. Little, "X-radiation-induced Transformation in a C3H Mouse Embryo-derived Cell Line," *Cancer Research* **36**, 1367-1374 (1976).
78. D. P. Heller and G. P. Raaphorst, "The Kinetics of Cellular Recovery in Exponential and Plateau Growth Phase Human Glioma Cells Following Gamma-Irradiation," *Int. J. Radiat. Oncol. Biol. Phys.* **30**, 383-390 (1994).
79. P. Lambin, B. Fertil, E. P. Malaise, and M. C. Joiner, "Multiphasic survival curves for cells of human tumor cell lines: Induced repair or hypersensitive subpopulation," *Radiat. Res.* **138**, S32-S36 (1994).
80. W. K. Sinclair, "Protection by Cysteamine against Lethal X-ray Damage during the cell Cycle of Chinese Hamster Cells," *Radiat. Res.* **39**, 135-154 (1969).
81. J. Denekamp and B. Littbrand, "[Angiogenesis--a new field for cancer therapy]," *Lakartidningen* **88**, 3788-3790 (1991).
82. J. Denekamp, "The current status of targeting tumour vasculature as a means of cancer therapy: an overview," *Int. J. Radiat. Biol.* **60**, 401-408 (1991).
83. J. Denekamp, "Inadequate vasculature in solid tumours: consequences for cancer research strategies," *BJR Suppl* **24**, 111-117 (1992).
84. J. Denekamp, "Review article: angiogenesis, neovascular proliferation and vascular pathophysiology as targets for cancer therapy," *Br. J. Radiol.* **66**, 181-196 (1993).
85. J. Denekamp, A. Dasu, and A. Waites, "Vasculature and microenvironmental gradients: the missing links in novel approaches to cancer therapy?" *Adv. Enzyme Regul.* **38**, 281-299 (1998).
86. J. Denekamp, "The tumour microcirculation as a target in cancer therapy: a clearer perspective," *Eur. J. Clin. Invest* **29**, 733-736 (1999).

87. J. Calkins, "Alternative repair models capable of generating shouldered dose-response curves (Letter)," *Int. J. Radiat. Biol.* **59**, 997-999 (1990).
88. D. T. Goodhead, "Saturable Repair Models of Radiation Action in Mammalian Cells," *Radiat. Res.* **104**, S58-S67 (1985).
89. R. H. Haynes, "The Interpretation of Microbial Inactivation and Recovery Phenomena," *Radiat. Res. Supplement* **6**, 1-29 (1966).
90. J. Calkins, "A method of Analysis of Radiation Response Based on Enzyme Kinetics," *Radiat. Res.* **45**, 50-62 (1971).
91. A. Sanchez-Reyes, "A Simple Model of Radiation Action in Cells Based on a Repair Saturation Mechanism," *Radiat. Res.* **130**, 139-147 (1992).
92. E. L. Powers, "Considerations of survival curves and target theory," *Phys. Med. Biol.* **3**, 3-28 (1962).
93. A. Sanches-Reyes, B. Farrus, and A. Biete, "A New Theoretical Formula for Fractionated Radiotherapy Based on a Saturable Cellular Repair Mechanism," *Acta Oncologica* **32**, 57-62 (1993).
94. A. Kappos and W. Pohlit, "A cybernetic model for radiation reactions in living cells," *Int. J. Radiat. Biol.* **22**, 51-65 (1972).
95. C.A. Tobias, "The Repair-misrepair model in radiobiology: comparison to other models," *Radiat. Res.* **104**, S-77-S-95 (1985).
96. N. Albright, "A Markov formulation of the repair-misrepair model of cell survival," *Radiat. Res.* **118**, 1-20 (1989).
97. S. B. Curtis, "Lethal and potentially lethal lesions induced by radiation--a unified repair model," *Radiat. Res.* **106**, 252-270 (1986).
98. R. D. Stewart, "Two-lesion kinetic model of double-strand break rejoining and cell killing," *Radiat. Res.* **156**, 365-378 (2001).

99. M. Guerrero, R. D. Stewart, J. Z. Wang, and X. A. Li, "Equivalence of the linear-quadratic and two-lesion kinetic models," *Phys. Med. Biol.* **47**, 3197-3209 (2001).
100. B. Emami, J. T. Lyman, A. Brown, L. Coia, M. Goitein, J. E. Munzenrider, B. Shank, L. J. Solin, and M. Wesson, "Tolerance of normal tissue to therapeutic irradiation," *Int. J. Radiat. Oncol. Biol. Phys.* **21**, 109-122 (1991).
101. C. Burman, G. J. Kutcher, B. Emami, and M. Goitein, "Fitting of normal tissue tolerance data to an analytic function," *Int. J. Radiat. Oncol. Biol. Phys.* **21**, 123-135 (1991).
102. G. J. Kutcher, C. Burman, L. Brewster, M. Goitein, and R. Mohan, "Histogram reduction method for calculating complication probabilities for three-dimensional treatment planning evaluations," *Int. J. Radiat. Oncol. Biol. Phys.* **21**, 137-146 (1991).
103. A. Niemierko and M. Goitein, "Calculation of normal tissue complication probability and dose-volume histogram reduction schemes for tissue with a critical element architecture," *Radiother. Oncol.* **20**, 166-176 (1991).
104. R. Mohan, G. S. Mageras, B. Baldwin, L. Brewster, G. J. Kutcher, S. Leibel, C. Burman, C. C. Ling, and Z. Fuks, "Clinically relevant optimization of 3-D conformal treatments," *Med. Phys.* **19**, 933-944 (1992).
105. A. Jackson, G. J. Kutcher, and E. D. Yorke, "Probability of radiation-induced complications for normal tissues with parallel architecture subject to non-uniform irradiation," *Med. Phys.* **20**, 613-625 (1993).
106. A. Niemierko and M. Goitein, "Modeling of normal tissue response to radiation: the critical volume model," *Int. J. Radiat. Oncol. Biol. Phys.* **25**, 135-145 (1992).
107. E. D. Yorke, G. J. Kutcher, and C. C. Ling, "Probability of radiation-induced complications in normal tissues with parallel architecture under conditions of uniform whole or partial organ irradiation," *Radiother. Oncol.* **26**, 226-237 (1993).

108. K. M. Haustermans, I. Hofland, and H. Van Poppel, "Cell kinetic measurements in prostate cancer," *Int. J. Radiat. Oncol. Biol. Phys.* **37**, 1067-1070 (1997).
109. D. L. Scrivner, J. S. Meyer, and N. Rujanavech, "Cell kinetics by bromodeoxyuridine labeling deoxyribonucleic acid ploidy in prostatic carcinoma biopsies," *J. Urol.* **146**, 1034-1039 (1991).