

Radiobiological Modelling In Radiation Oncology

Radiation therapy (RT) plays a crucial role in the management of cancer, however, current standards of care have yet to account for patient specific radiation sensitivity. Raman spectroscopy (RS) is a promising technique for radiobiological studies as a way to measure radiation responses in biological samples and could provide a method for monitoring and predicting radiation response in patients. The work in this dissertation gives way to significant advances in the implementation of RS for applications in radiation oncology. Specifically, instrumentation improvements for clinical implementation of RS were achieved through the investigation and development of Raman microfluidic systems. Unique magnesium fluoride based microfluidic systems were engineered and evaluated for applications in radiobiological studies. These systems were found to yield superior spectral quality over traditional microfluidic designs. Furthermore, in order to assert RS as a key technique for clinical monitoring and prediction of radiation responses, human non-small cell lung cancer (NSCLC) and breast adenocarcinoma tumour xenograft models were investigated for Raman signatures of radiation response. These studies found that RS can identify unique and distinct signatures of radiation response in tumours, that can be tracked over time. In particular, NSCLC tumours were found to have key radiation induced modulations in cell cycle and metabolic linked spectral features- including glycogen. Breast adenocarcinoma tumours were found to exhibit distinct fluctuations in spectral features linked to cell cycle as well as protein content. In the case of NSCLC, radiation response signatures were found to be linked to tumour regression and

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hypoxic status of the tumour- a key factor that dictates radiation resistance in the disease. This work provides the first application of RS to measure radiation response signatures of tumours irradiated *\textit{in vivo}*. These results show that RS is a versatile technique that can offer insight into radiation induced molecular changes that are unique to the type of cancer and can be monitored over several days following radiation exposure. Together with improved instrumentation for radiobiological studies using microfluidics, the work presented in this dissertation further emphasizes the key role RS can have in radiation oncology and personalization of RT.

This practical, up-to-date, bedside-oriented radiation oncology book encompasses the essential aspects of the subject with coverage on radiation physics, radiobiology, and clinical radiation oncology. The first two sections examine concepts that are crucial in radiation physics and radiobiology. The third section describes radiation treatment regimens appropriate for the main cancer sites and tumor types. Translational research in oncology benefits from an abundance of knowledge resulting from genome-scale studies concerning the molecular pathways involved in tumorigenesis. Translational oncology represents a bridge between basic research and clinical practice in cancer medicine. The vast majority of cancer cases are due to environmental risk factors. Many of these environmental factors are controllable lifestyle choices. Experimental cancer treatments are studied in clinical trials to compare the proposed treatment to the best existing treatment through translational research. The key features of the book include:

- 1) New screening for the development of radioprotectors: radioprotection and anti-cancer effect of β -Glucan (*Enterococcus faecalis*)
- 2) Translational perspective on hepatocellular carcinoma
- 3) Brachytherapy for endometrial

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cancer 4) Discovery of small molecule inhibitors for histone methyltransferases in cancer

The treatment of a patient with radiation therapy is planned to find the optimal way to treat a tumour while minimizing the dose received by the surrounding normal tissues. In order to better exploit the possibilities of this process, the availability of accurate and quantitative knowledge of the peculiar responses of the different tissues is of paramount importance. This book provides an invaluable tutorial for radiation oncologists, medical physicists, and dosimetrists involved in the planning optimization phase of treatment. It presents a practical, accessible, and comprehensive summary of the field's current research and knowledge regarding the response of normal tissues to radiation. This is the first comprehensive attempt to do so since the publication of the QUANTEC guidelines in 2010. Features: Addresses the lack of systemization in the field, providing educational materials on predictive models, including methods, tools, and the evaluation of uncertainties Collects the combined effects of features, other than dose, in predicting the risk of toxicity in radiation therapy Edited by two leading experts in the field The move towards individually-optimised treatments, using knowledge of normal tissue and tumour radiosensitivity, proliferation rates, etc, in combination with three-dimensional planning, will need mathematical modelling to achieve its full potential. This modelling process will also be capable of helping develop a rational and cost-effective use of resources. Amongst radiation oncologists and medical physicists there is a need for a greater understanding of the scope, applications and limitations of radiobiological modelling, particularly in complex situations that include multiple treatment variables, the respective influence of which are difficult to separate out by randomised trials without using radiobiologically-based analysis. In future there will be

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increasing use of modelling in practical situations, including treatment gap corrections, normal tissue tolerance predictions, optimisation of therapy determined by predictive assays, multi-modality schedule design, the simulation of clinical trials, testing contemporaneous medico-legal problems and teaching general principals of radiotherapy. Stereotactic body radiation therapy (SBRT) has emerged as an important innovative treatment for various primary and metastatic cancers. This book provides a comprehensive and up-to-date account of the physical/technological, biological, and clinical aspects of SBRT. It will serve as a detailed resource for this rapidly developing treatment modality. The organ sites covered include lung, liver, spine, pancreas, prostate, adrenal, head and neck, and female reproductive tract. Retrospective studies and prospective clinical trials on SBRT for various organ sites from around the world are examined, and toxicities and normal tissue constraints are discussed. This book features unique insights from world-renowned experts in SBRT from North America, Asia, and Europe. It will be necessary reading for radiation oncologists, radiation oncology residents and fellows, medical physicists, medical physics residents, medical oncologists, surgical oncologists, and cancer scientists.

Common factors that lead to treatment failure in head and neck cancer are the lack of tumour oxygenation, the accelerated division of cancer cells during treatment, and radioresistance. These tumour-related challenges and possible ways to overcome them are covered in this book, authored by three medical physicists and a clinical oncologist who explain how different radiobiological findings have led to the development of various treatment techniques for head and neck cancer. Novel treatment techniques as supported by current scientific evidence are comprehensively explored, as well as the major challenges that arise in the retreatment

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of patients who have already undergone a form of radiotherapy for primary head and neck cancer. Features: Uses an interdisciplinary approach, encompassing clinical aspects of radiotherapy, radiation biology, and medical physics Applies content by relating all radiobiological characteristics to their respective clinical implications Explains the radiobiological rationale for all previous and current clinical trials for head and neck cancer

Understand Quantitative Radiobiology from a Radiation Biophysics Perspective In the field of radiobiology, the linear-quadratic (LQ) equation has become the standard for defining radiation-induced cell killing. Radiotherapy Treatment Planning: Linear-Quadratic Radiobiology describes tumor cell inactivation from a radiation physics perspective and offers appropriate LQ parameters for modeling tumor and normal tissue responses. Explore the Latest Cell Killing Numbers for Defining Iso-Effective Cancer Treatments The book compiles radiation mechanism information from biophysical publications of the past 50 years, addressing how ionizing radiation produces the killing of stem cells in human tumors. It presents several physical and chemical parameters that can modulate the radiation response of clonogenic cells in tumors. The authors describe the use of the LQ model in basic radiation mechanism studies with cells of relatively homogeneous radiation response and then extend the model to the fitting of survival data generated with heterogeneous cell populations (tumors). They briefly discuss how to use the LQ model for predicting tumor (local) control probability (TCP) and normal tissue complication probability (NTCP). The book also examines potential molecular targets related to alpha- and beta-inactivation and gives suggestions for further molecular characterizations of these two independent processes. Develop Efficacious, Patient-Friendly Treatments at Reduced Costs Focusing on quantitative radiobiology in

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LQ formulation, this book assists medical physicists and radiation oncologists in identifying improved cancer treatments. It also encourages investigators to translate potentially improved radiotherapy schedules based on TCP and NTCP modeling into actual patient benefit.

This publication is aimed at students and teachers involved in teaching programmes in field of medical radiation physics, and it covers the basic medical physics knowledge required in the form of a syllabus for modern radiation oncology. The information will be useful to those preparing for professional certification exams in radiation oncology, medical physics, dosimetry or radiotherapy technology.

Motivated by the explosion of molecular data on humans-particularly data associated with individual patients-and the sense that there are large, as-yet-untapped opportunities to use this data to improve health outcomes, *Toward Precision Medicine* explores the feasibility and need for "a new taxonomy of human disease based on molecular biology" and develops a potential framework for creating one. The book says that a new data network that integrates emerging research on the molecular makeup of diseases with clinical data on individual patients could drive the development of a more accurate classification of diseases and ultimately enhance diagnosis and treatment. The "new taxonomy" that emerges would define diseases by their underlying molecular causes and other factors in addition to their traditional physical signs and symptoms. The book adds that the new data network could also improve biomedical research by enabling scientists to access patients' information during treatment while still protecting their rights. This would allow the marriage of molecular research and clinical data at the point of care, as opposed to research information continuing to reside primarily in academia. *Toward Precision Medicine* notes that moving toward individualized medicine requires

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that researchers and health care providers have access to very large sets of health- and disease-related data linked to individual patients. These data are also critical for developing the information commons, the knowledge network of disease, and ultimately the new taxonomy.

Imaging is crucial in the multidisciplinary approach to head and neck cancer management. The rapid technological development of recent years makes it necessary for all members of the multidisciplinary team to understand the potential applications, limitations, and advantages of existing and evolving imaging technologies. It is equally important that the radiologist has sufficient clinical background knowledge to understand the clinical significance of imaging findings. This book provides an overview of the findings obtained using different imaging techniques during the evaluation of head and neck neoplasms, both before and after therapy. All anatomic areas in the head and neck are covered, and the impact of imaging on patient management is discussed in detail. The authors are recognized experts in the field, and numerous high-quality images are included. This second edition provides information on the latest imaging developments in this area, including the application of PET-CT and diffusion-weighted magnetic resonance imaging. In print since 1972, this seventh edition of *Radiobiology for the Radiologist* is the most extensively revised to date. It consists of two sections, one for those studying or practicing diagnostic radiology, nuclear medicine and radiation oncology; the other for those engaged in the study or clinical practice of radiation oncology--a new chapter, on radiologic terrorism, is specifically for those in the radiation sciences who would manage exposed individuals in the event of a terrorist event. The 17 chapters in Section I represent a general introduction to radiation biology and a complete, self-contained course especially for residents in diagnostic radiology and nuclear

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medicine that follows the Syllabus in Radiation Biology of the RSNA. The 11 chapters in Section II address more in-depth topics in radiation oncology, such as cancer biology, retreatment after radiotherapy, chemotherapeutic agents and hyperthermia. Now in full color, this lavishly illustrated new edition is replete with tables and figures that underscore essential concepts. Each chapter concludes with a "summary of pertinent conclusions" to facilitate quick review and help readers retain important information.

This concise but comprehensive textbook sets out the essentials of the science and clinical application of radiobiology for those seeking accreditation in radiation oncology, clinical radiation physics and radiation technology. Fully revised and updated to keep abreast of current developments in radiation biology and radiation oncology, the fourth edition continues to present in an interesting way the biological basis of radiation therapy, discussing the basic principles and significant developments that underlie the latest attempts to improve the radiotherapeutic management of cancer. New topics for the fourth edition include chapters on the mechanisms of cell death, biological response modifiers, and biological image guided radiotherapy, with major revisions to sections on the molecular basis of the radiation response, tumour hypoxia and the dose-rate effect. A variety of new authors have contributed to this revision, who, together with the new Editorial team, have used their significant international teaching experience to ensure the content remains clear and comprehensive, and as valuable to the trainee as it is to the established radiation oncologist. With the fourth edition we will see the most radical change so far - as Professor Gordon Steel has retired as Editor and has been replaced by Bert van der Kogel, the current current course director for the above-mentioned course, plus Michael Joiner, who is the head of the Radiation Biology Program at

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the Wayne State University and is the Associate Editor of the International Journal of Radiation Biology.

The scientific and clinical foundations of Radiation Therapy are cross-disciplinary. This book endeavours to bring together the physics, the radiobiology, the main clinical aspects as well as available clinical evidence behind Radiation Therapy, presenting mutual relationships between these disciplines and their role in the advancements of radiation oncology.

Gain mastery over the fundamentals of radiation oncology physics! This package gives you over 60 tutorial videos (each 15-20 minutes in length) with a companion text, providing the most complete and effective introduction available. Dr. Ford has tested this approach in formal instruction for years with outstanding results. The text includes extensive problem sets for each chapter. The videos include embedded quizzes and "whiteboard" screen technology to facilitate comprehension.

Together, this provides a valuable learning tool both for training purposes and as a refresher for those in practice. Key Features A complete learning package for radiation oncology physics, including a full series of video tutorials with an associated textbook companion website Clearly drawn, simple illustrations throughout the videos and text Embedded quiz feature in the video tutorials for testing comprehension while viewing Each chapter includes problem sets (solutions available to educators)

Modern medical imaging and radiation therapy technologies are so complex and computer driven that it is difficult for physicians and technologists to know exactly what is happening at the point-of-care. Medical physicists responsible for filling this gap in knowledge must stay abreast of the latest advances at the intersection of medical imaging and radiation therapy. This book provides medical physicists and radiation oncologists current and relevant information on Adaptive Radiation Therapy (ART), a state-of-the-art approach that

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uses a feedback process to account for patient-specific anatomic and/or biological changes, thus delivering highly individualized radiation therapy for cancer patients. The book should also benefit medical dosimetrists and radiation therapists. Adaptive Radiation Therapy describes technological and methodological advances in the field of ART, as well as initial clinical experiences using ART for selected anatomic sites. Divided into three sections (radiobiological basis, current technologies, and clinical applications), the book covers: Morphological and biological biomarkers for patient-specific planning Design and optimization of treatment plans Delivery of IMRT and IGRT intervention methodologies of ART Management of intrafraction variations, particularly with respiratory motion Quality assurance needed to ensure the safe delivery of ART ART applications in several common cancer types / anatomic sites The technology and methodology for ART have advanced significantly in the last few years and accumulated clinical data have demonstrated the need for ART in clinical settings, assisted by the wide application of intensity modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT). This book shows the real potential for supplying every patient with individualized radiation therapy that is maximally accurate and precise.

- Summarizes the state of the art in the most relevant areas of medical physics and engineering applied to radiation oncology
- Covers all relevant areas of the subject in detail, including 3D imaging and image processing, 3D treatment planning, modern treatment techniques, patient positioning, and aspects of verification and quality assurance
- Conveys information in a readily understandable way that will appeal to professionals and students with a medical background

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as well as to newcomers to radiation oncology from the field of physics

Practical Radiobiology for Proton Therapy Planning covers the principles, advantages and potential pitfalls that occur in proton therapy, especially its radiobiological modelling applications. This book is intended to educate, inform and to stimulate further research questions.

Additionally, it will help proton therapy centres when designing new treatments or when unintended errors or delays occur. The clear descriptions of useful equations for high LET particle beam applications, worked examples of many important clinical situations, and discussion of how proton therapy may be optimized are all important features of the text. This important book blends the relevant physics, biology and medical aspects of this multidisciplinary subject.

The mathematical models in this book are concerned with a variety of approaches to the manner in which the clinical radiologic treatment of human neoplasms can be improved. These improvements comprise ways of delivering radiation to the malignancies so as to create considerable damage to tumor cells while sparing neighboring normal tissues. There is no unique way of dealing with these improvements. Accordingly, in this book a number of different presentations are given. Each presentation has as its goal some aspect of the improvement, or optimization, of radiotherapy. This book is a collection of current ideas concerned with the optimization of human cancer radiotherapy. It is hoped that readers will build on this collection and develop superior approaches for the understanding of the ways to

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improve therapy. The author owes a special debt of thanks to Kathy Prindle who breezed through the typing of this book with considerable dexterity. TABLE OF CONTENTS Chapter GENERAL INTRODUCTION 1. 1 Introduction 1 1. 2 History of Cancer and its Treatment by Radiotherapy 8 1. 3 Some Mathematical Models of Tumor Growth 12 1. 4 Spatial Distribution of the Radiation Dose 20 Chapter 2 SURVIVAL CURVES FROM STATISTICAL MODELS 24 2. 1 Introduction 24 2. 2 The Target Model 26 2. 3 Single-hit-to-kill Model 27 2. 4 Multitarget, Single-hit Survival 29 2. 5 Multitarget, Multihit Survival 31 2. 6 Single-target, Multihit Survival 31 2.

This book provides a complete overview of the role of machine learning in radiation oncology and medical physics, covering basic theory, methods, and a variety of applications in medical physics and radiotherapy. An introductory section explains machine learning, reviews supervised and unsupervised learning methods, discusses performance evaluation, and summarizes potential applications in radiation oncology. Detailed individual sections are then devoted to the use of machine learning in quality assurance; computer-aided detection, including treatment planning and contouring; image-guided radiotherapy; respiratory motion management; and treatment response modeling and outcome prediction. The book will be invaluable for students and residents in medical physics and radiation oncology and will also appeal to more experienced practitioners and researchers and members of applied machine learning communities.

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This book explores outcome modeling in cancer from a data-centric perspective to enable a better understanding of complex treatment response, to guide the design of advanced clinical trials, and to aid personalized patient care and improve their quality of life. It contains coverage of the relevant data sources available for model construction (panomics), ranging from clinical or preclinical resources to basic patient and treatment characteristics, medical imaging (radiomics), and molecular biological markers such as those involved in genomics, proteomics and metabolomics. It also includes discussions on the varying methodologies for predictive model building with analytical and data-driven approaches. This book is primarily intended to act as a tutorial for newcomers to the field of outcome modeling, as it includes in-depth how-to recipes on modeling artistry while providing sufficient instruction on how such models can approximate the physical and biological realities of clinical treatment. The book will also be of value to seasoned practitioners as a reference on the varying aspects of outcome modeling and their current applications. Features: Covers top-down approaches applying statistical, machine learning, and big data analytics and bottom-up approaches using first principles and multi-scale techniques, including numerical simulations based on Monte Carlo and automata techniques Provides an overview of the available software tools and resources for outcome model development and evaluation, and includes hands-on detailed examples throughout Presents a diverse selection of the common applications of outcome

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modeling in a wide variety of areas: treatment planning in radiotherapy, chemotherapy and immunotherapy, utility-based and biomarker applications, particle therapy modeling, oncological surgery, and the design of adaptive and SMART clinical trials

Practical Clinical Oncology, 2nd edition, provides a practical and comprehensive review of the current management of common types of cancer. Introductory chapters give background information on the main treatment modalities and other key issues such as acute oncology, palliative care and clinical research, with new chapters on pathology and advanced external beam radiotherapy. Subsequent chapters describe the diagnosis and treatment of malignancies, based on tumour site or type. Finally, multiple choice questions allow the reader to test their knowledge. This edition has been fully updated to reflect the most current developments in radiotherapy, tumour biology and drug therapy. With an emphasis on practical aspects of cancer care that will be relevant to day-to-day decision making, this book is an invaluable resource on contemporary clinical management of the cancer patient for all trainees and practitioners involved in clinical oncology, medical oncology and palliative care, as well as for specialist nurses and radiographers.

The aim of this book is to provide a uniquely comprehensive source of information on the entire field of radiation therapy physics. The very significant advances in imaging, computational, and accelerator technologies receive full consideration, as do such topics as the dosimetry of radiolabeled antibodies and dose

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calculation models. The scope of the book and the expertise of the authors make it essential reading for interested physicians and physicists and for radiation dosimetrists.

Details technology associated with radiation oncology, emphasizing design of all equipment allied with radiation treatment. Describes procedures required to implement equipment in clinical service, covering needs assessment, purchase, acceptance, and commissioning, and explains quality assurance issues. Also addresses less common and evolving technologies. For medical physicists and radiation oncologists, as well as radiation therapists, dosimetrists, and engineering technologists. Includes b&w medical images and photos of equipment. Cancer is a widespread type of diseases that each year affects millions of people. It is mainly treated by chemotherapy, surgery or radiation therapy, or a combination of them. One modality of radiation therapy is high dose-rate brachytherapy, used in treatment of for example prostate cancer and gynecologic cancer. Brachytherapy is an invasive treatment in which catheters (hollow needles) or applicators are used to place the highly active radiation source close to or within a tumour. The treatment planning problem, which can be modelled as a mathematical optimization problem, is the topic of this thesis. The treatment planning includes decisions on how many catheters to use and where to place them as well as the dwell times for the radiation source. There are multiple aims with the treatment and these are primarily to give the tumour a radiation dose that is sufficiently high and to give the surrounding healthy tissue and organs (organs at risk) a dose that is sufficiently low. Because these aims are in conflict, modelling the treatment planning gives

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optimization problems which essentially are multiobjective. To evaluate treatment plans, a concept called dosimetric indices is commonly used and they constitute an essential part of the clinical treatment guidelines. For the tumour, the portion of the volume that receives at least a specified dose is of interest while for an organ at risk it is rather the portion of the volume that receives at most a specified dose. The dosimetric indices are derived from the dose-volume histogram, which for each dose level shows the corresponding dosimetric index. Dose-volume histograms are commonly used to visualise the three-dimensional dose distribution. The research focus of this thesis is mathematical modelling of the treatment planning and properties of optimization models explicitly including dosimetric indices, which the clinical treatment guidelines are based on. Modelling dosimetric indices explicitly yields mixedinteger programs which are computationally demanding to solve. The computing time of the treatment planning is of clinical relevance as the planning is typically conducted while the patient is under anaesthesia. Research topics in this thesis include both studying properties of models, extending and improving models, and developing new optimization models to be able to take more aspects into account in the treatment planning. There are several advantages of using mathematical optimization for treatment planning in comparison to manual planning. First, the treatment planning phase can be shortened compared to the time consuming manual planning. Secondly, also the quality of treatment plans can be improved by using optimization models and algorithms, for example by considering more of the clinically relevant aspects. Finally, with the use of optimization algorithms the requirements of experience and skill level for the planners are lower. This thesis summary contains a literature review over optimization models for treatment planning, including the catheter placement

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problem. How optimization models consider the multiobjective nature of the treatment planning problem is also discussed. Proton and Carbon Ion Therapy is an up-to-date guide to using proton and carbon ion therapy in modern cancer treatment. The book covers the physics and radiobiology basics of proton and ion beams, dosimetry methods and radiation measurements, and treatment delivery systems. It gives practical guidance on patient setup, target localization, and treatment planning for clinical proton and carbon ion therapy. The text also offers detailed reports on the treatment of pediatric cancers, lymphomas, and various other cancers. After an overview, the book focuses on the fundamental aspects of proton and carbon ion therapy equipment, including accelerators, gantries, and delivery systems. It then discusses dosimetry, biology, imaging, and treatment planning basics and provides clinical guidelines on the use of proton and carbon ion therapy for the treatment of specific cancers. Suitable for anyone involved with medical physics and radiation therapy, this book offers a balanced and critical assessment of state-of-the-art technologies, major challenges, and the future outlook of proton and carbon ion therapy. It presents a thorough introduction for those new to the field while providing a helpful, up-to-date reference for readers already using the therapy in clinical settings. This book serves as a practical guide for the use of carbon ions in cancer radiotherapy. On the basis of clinical experience with more than 7,000 patients with various types of tumors treated over a period of nearly 20 years at the National Institute of Radiological Sciences, step-by-step procedures and technological development of this modality are highlighted. The book is divided into two sections, the first covering the underlying principles of physics and biology, and the second section is a systematic review by tumor site, concentrating on the role of therapeutic techniques and the

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pitfalls in treatment planning. Readers will learn of the superior outcomes obtained with carbon-ion therapy for various types of tumors in terms of local control and toxicities. It is essential to understand that the carbon-ion beam is like a two-edged sword: unless it is used properly, it can increase the risk of severe injury to critical organs. In early series of dose-escalation studies, some patients experienced serious adverse effects such as skin ulcers, pneumonitis, intestinal ulcers, and bone necrosis, for which salvage surgery or hospitalization was required. To preclude such detrimental results, the adequacy of therapeutic techniques and dose fractionations was carefully examined in each case. In this way, significant improvements in treatment results have been achieved and major toxicities are no longer observed. With that knowledge, experts in relevant fields expand upon techniques for treatment delivery at each anatomical site, covering indications and optimal treatment planning. With its practical focus, this book will benefit radiation oncologists, medical physicists, medical dosimetrists, radiation therapists, and senior nurses whose work involves radiation therapy, as well as medical oncologists and others who are interested in radiation therapy.

Basic Clinical Radiobiology is a concise but comprehensive textbook setting out the essentials of the science and clinical application of radiobiology for those seeking accreditation in radiation oncology, clinical radiation physics, and radiation technology. Fully revised and updated to keep abreast of current developments in radiation biology and radiation oncology, this fifth edition continues to present in an interesting way the biological basis of radiation therapy, discussing the basic principles and significant developments that underlie the latest attempts to improve the radiotherapeutic management of cancer. This new edition is highly illustrated with attractive 2-colour presentation and now

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includes new chapters on stem cells, tissue response and the convergence of radiotherapy, radiobiology, and physics. It will be invaluable for FRCR (clinical oncology) and equivalent candidates, SpRs (and equivalent) in radiation oncology, practicing radiation oncologists and radiotherapists, as well as radiobiologists and radiotherapy physicists.

Cancer is a widespread class of diseases that each year affects millions of people. It is mostly treated with chemotherapy, surgery, radiation therapy, or combinations thereof. High dose rate (HDR) brachytherapy (BT) is one modality of radiation therapy, which is used to treat for example prostate cancer and gynecologic cancer. In BT, catheters (i.e., hollow needles) or applicators are used to place a single, small, but highly radioactive source of ionizing radiation close to or within a tumour, at dwell positions. An emerging technique for HDR BT treatment is intensity modulated brachytherapy (IMBT), in which static or dynamic shields are used to further shape the dose distribution, by hindering the radiation in certain directions. The topic of this thesis is the application of mathematical optimization to model and solve the treatment planning problem. The treatment planning includes decisions on catheter placement, that is, how many catheters to use and where to place them, as well as decisions for dwell times. Our focus is on the latter decisions. The primary treatment goals are to give the tumour a sufficiently high radiation dose while limiting the dose to the surrounding healthy organs, to avoid severe side effects. Because these aims are typically in conflict, optimization models of the treatment planning problem are inherently multiobjective. Compared to manual treatment planning, there are several advantages of using mathematical optimization for treatment planning. First, the optimization of treatment plans requires less time, compared to the time-consuming manual planning. Secondly, treatment plan quality can be

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improved by using optimization models and algorithms. Finally, with the use of sophisticated optimization models and algorithms the requirements of experience and skill level for the planners are lower. The use of optimization for treatment planning of IMBT is especially important because the degrees of freedom are too many for manual planning. The contributions of this thesis include the study of properties of treatment planning models, suggestions for extensions and improvements of proposed models, and the development of new optimization models that take clinically relevant, but uncustomary aspects, into account in the treatment planning. A common theme is the modelling of constraints on dosimetric indices, each of which is a restriction on the portion of a volume that receives at least a specified dose, or on the lowest dose that is received by a portion of a volume. Modelling dosimetric indices explicitly yields mixed-integer programs which are computationally demanding to solve. We have therefore investigated approximations of dosimetric indices, for example using smooth non-linear functions or convex functions. Contributions of this thesis are also a literature review of proposed treatment planning models for HDR BT, including mathematical analyses and comparisons of models, and a study of treatment planning for IMBT, which shows how robust optimization can be used to mitigate the risks from rotational errors in the shield placement.

Cancer är en grupp av sjukdomar som varje år drabbar miljontals människor. De vanligaste behandlingsformerna är cellgifter, kirurgi, strålbehandling eller en kombination av dessa. I denna avhandling studeras högdosrat brachyterapi (HDR BT), vilket är en form av strålbehandling som till exempel används vid behandling av prostatacancer och gynekologisk cancer. Vid brachyterapi används ihåliga nålar eller applikatorer för att placera en millimeterstor strålkälla antingen inuti eller intill en tumör. I varje nål finns det ett antal

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så kallade dröjpositioner där strålkällan kan stanna en viss tid för att bestråla den omkringliggande vävnaden, i alla riktningar. Genom att välja lämpliga tider för dröjpositionerna kan dosfördelningen formas efter patientens anatomi. Utöver HDR BT studeras också den nya tekniken intensitetsmodulerad brachyterapi (IMBT) vilket är en variation på HDR BT där skärmning används för att minska strålningen i vissa riktningar vilket gör det möjligt att forma dosfördelningen bättre. Planeringen av en behandling med HDR BT omfattar hur många nålar som ska användas, var de ska placeras samt hur länge strålkällan ska stanna i de olika dröjpositionerna. För HDR BT kan dessa vara flera hundra stycken medan det för IMBT snarare handlar om tusentals möjliga kombinationer av dröjpositioner och inställningar av skärmarna. Planeringen resulterar i en dosplan som beskriver hur hög stråldos som tumören och intilliggande frisk vävnad och riskorgan utsätts för. Dosplaneringen kan formuleras som ett matematiskt optimeringsproblem vilket är ämnet för avhandlingen. De övergripande målsättningarna för behandlingen är att ge en tillräckligt hög stråldos till tumören, för att döda alla cancerceller, samt att undvika att bestråla riskorgan eftersom det kan ge allvarliga biverkningar. Då alla målsättningarna inte samtidigt kan uppnås fullt ut så fås optimeringsproblem där flera målsättningar behöver prioriteras mot varandra. Utöver att dosplanen uppfyller kliniska behandlingsriktlinjer så är också tidsaspekten av planeringen viktig eftersom det är vanligt att den görs medan patienten är bedövad eller sövd. Vid utvärdering av en dosplan används dos-volyymmått. För en tumör anger ett dosvolyymmått hur stor andel av tumören som får en stråldos som är högre än en specificerad nivå. Dos-volyymmått utgör en viktig del av målen för dosplaner som tas upp i kliniska behandlingsriktlinjer och ett exempel på ett sådant mål vid behandling av prostatacancer är att 95% av prostatans volym

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ska få en stråldos som är minst den föreskrivna dosen. Dos-volyymmått utläses ur de kliniskt betydelsefulla dos-volym histogrammen som för varje stråldosnivå anger motsvarande volym som erhåller den dosen. En fördel med att använda matematisk optimering för dosplanering är att det kan spara tid jämfört med manuell planering. Med väl utvecklade modeller så finns det också möjlighet att skapa bättre dosplaner, till exempel genom att riskorganen nås av en lägre dos men med bibehållen dos till tumören. Vidare så finns det även fördelar med en process som inte är lika personberoende och som inte kräver erfarenhet i lika stor utsträckning som manuell dosplanering i dagsläget gör. Vid IMBT är det dessutom så många frihetsgrader att manuell planering i stort sett blir omöjligt. I avhandlingen ligger fokus på hur dos-volyymmått kan användas och modelleras explicit i optimeringsmodeller, så kallade dos-volymmodeller. Detta omfattar såväl analys av egenskaper hos befintliga modeller, utvidgningar av tidigare använda modeller samt utveckling av nya optimeringsmodeller. Eftersom dos-volymmodeller modelleras som heltalsproblem, vilka är beräkningskrävande att lösa, så är det också viktigt att utveckla algoritmer som kan lösa dem tillräckligt snabbt för klinisk användning. Ett annat mål för modellutvecklingen är att kunna ta hänsyn till fler kriterier som är kliniskt relevanta men som inte ingår i dos-volymmodeller. En sådan kategori av mått är hur dosen är fördelad rumsligt, exempelvis att volymen av sammanhängande områden som får en alldeles för hög dos ska vara liten. Sådana områden går dock inte att undvika helt eftersom det är typiskt för dosplaner för brachyterapi att stråldosen fördelar sig ojämnt, med väldigt höga doser till små volymer precis intill strålkällorna. Vidare studeras hur små fel i inställningarna av skärmningen i IMBT påverkar dosplanens kvalitet och de olika utvärderingsmått som används kliniskt. Robust optimering har använts för att

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säkerställa att en dosplan tas fram som är robust sett till dessa möjliga fel i hur skärmningen är placerad. Slutligen ges en omfattande översikt över optimeringsmodeller för dosplanering av HDR BT och speciellt hur optimeringsmodellerna hanterar de motstridiga målsättningarna.

This book concisely reviews important advances in radiation oncology, providing practicing radiation oncologists with a fundamental understanding of each topic and an appreciation of its significance for the future of radiation oncology. It explores in detail the impact of newer imaging modalities, such as multiparametric magnetic resonance imaging (MRI) and positron emission tomography (PET) using fluorodeoxyglucose (FDG) and other novel agents, which deliver improved visualization of the physiologic and phenotypic features of a given cancer, helping oncologists to provide more targeted radiotherapy and assess the response. Due consideration is also given to how advanced technologies for radiation therapy delivery have created new treatment options for patients with localized and metastatic disease, highlighting the increasingly important role of image-guided radiotherapy in treating systemic and oligometastatic disease. Further topics include the potential value of radiotherapy in enhancing immunotherapy thanks to the broader immune-stimulatory effects, how cancer stem cells and the tumor microenvironment influence response, and the application of mathematical and systems biology methods to radiotherapy.

This book is a concise and well-illustrated review of the physics and biology of radiation therapy intended for radiation oncology residents, radiation therapists, dosimetrists, and physicists. It presents topics that are included on the Radiation Therapy Physics and Biology examinations and is designed with the intent of presenting information in an easily

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digestible format with maximum retention in mind. The inclusion of mnemonics, rules of thumb, and reader-friendly illustrations throughout the book help to make difficult concepts easier to grasp. Basic Radiotherapy Physics and Biology is a valuable reference for students and prospective students in every discipline of radiation oncology.

Radiobiological Modelling in Radiation Oncology
British Inst of Radiology

This new book educates readers about new technologies before they appear in hospitals, enabling medical physicists and clinicians to prepare for new technologies thoroughly and proactively, and provide better patient care once new equipment becomes available. Emerging technologies in imaging, treatment planning, treatment delivery, dosimetry and informatics are all discussed.

The book is divided into three parts: recently developed technologies available for practice; technologies under development nearing completion; and technologies in an early stage of development that could have potential radiotherapy applications. Features: Introduces emerging technologies in imaging, treatment planning, treatment delivery, dosimetry and informatics The advantages and limitations of each technology in clinical settings are discussed, and recommendations on how to adopt the technologies are provided Critiques and improvement points are provided for researchers, in addition to suggestions on how to prepare quality assurance are provided as needed

This text properly considers the most recent and relevant advances in molecular RB of GB, taking into account the related topics of pathobiology, and underscores the most promising translational perspectives from the preclinical

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to the clinical domain. Section I (From Bedside to Bench) discusses conditions associated with RT resistance of GB and the consequent RB hints, technology improvements intended to overcome RT-resistance of GB, mathematical modeling of RB parameters from clinical studies, the present impact of molecular prognostic factors in therapy of GB, and RT tolerance of normal brain. Section II (Preclinical Research and Pathobiology Topics) presents the traditional and mechanistic/molecular approaches to RB of GB, genetic and epigenetic studies on GB, issues of cell-death pathways, stem-like cells, invasiveness, tumor microenvironment, hypoxia, mi-RNA manipulations, and nanoparticle technology. Section III (Translational Perspectives) presents RB issues related to molecular profiling and classification of GB as frames of reference for clinical studies, translational perspectives of gene therapy, evolving protocols based on pre-clinical data and large data-bases and ontologic models.

Radiobiology of Glioblastoma: Recent Advances and Related Pathobiology will be of great value to pathologists, medical oncologists, radiation oncologists as well as basic researchers and clinical investigators. This book is designed to convey as much information as possible in a concise and simple way to make it suitable for students, researchers and clinical medical physicists. Better meanings, codes and examples are included. Most of the basics are also covered for easy reference along with a glossary of objective-type questions. Upon completion of this textbook, the readers will gather knowledge about the physics, chemistry and biology of

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the human body towards cancer treatment using radiation.

The industrial and medical applications of radiation have been augmented and scientific insight into mechanisms for radiation action notably progressed. In addition, the public concern about radiation risk has also grown extensively. Today the importance of risk communication among stakeholders involved in radiation-related issues is emphasized much more than any time in the past. Thus, the circumstances of radiation research have drastically changed, and the demand for a novel approach to radiation-related issues is increasing. It is thought that the publication of the book *Evolution of Ionizing Radiation Research* at this time would have enormous impacts on the society. The editor believes that technical experts would find a variety of new ideas and hints in this book that would be helpful to them to tackle ionizing radiation.

Clinical conformal radiotherapy is the holy grail of radiation treatment and is now becoming a reality through the combined efforts of physical scientists and engineers, who have improved the physical basis of radiotherapy, and the interest and concern of imaginative radiotherapists and radiographers. *Intensity-Modulated Radiation Therapy* describes in detail the physics germane to the development of a particular form of clinical conformal radiotherapy called intensity modulated radiation therapy (IMRT). IMRT has become a topic of tremendous importance in recent years and is now being seriously investigated for its potential to improve the outcome of radiation therapy. The book collates the state-

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of-the-art literature together with the author's personal research experience and that of colleagues in the field to produce a text suitable for new research workers, Ph.D. students, and practicing radiation physicists that require a thorough introduction to IMRT. Fully illustrated, indexed, and referenced, the book has been prepared in a form suitable for supporting a teaching course.

From background physics and biological models to the latest imaging and treatment modalities, the Handbook of Radiotherapy Physics: Theory and Practice covers all theoretical and practical aspects of radiotherapy physics. In this comprehensive reference, each part focuses on a major area of radiotherapy, beginning with an introduction by the editors and then subdividing into self-contained chapters. The first three parts present the fundamentals of the underlying physics, radiobiology, and technology involved. The ensuing sections discuss the support requirements of external beam radiotherapy, such as dose measurements, properties of clinical beams, patient dose computation, treatment planning, and quality assurance, followed by a part that explores exciting new advances that include developments in photon and particle therapy. Subsequent sections examine brachytherapy using sealed and unsealed sources and provide the framework of radiation protection, including an appendix that describes the detailed application of UK legislation. The final part contains handy tables of both physical constants and attenuation data. To achieve safe and effective radiotherapy, there needs to be a close understanding among various disciplines. With contributions from

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renowned specialists, the Handbook of Radiotherapy Physics: Theory and Practice provides essential theoretical and practical knowledge for medical physicists, researchers, radiation oncologists, and radiation technologists.

Comprehensive Biomedical Physics is a new reference work that provides the first point of entry to the literature for all scientists interested in biomedical physics. It is of particularly use for graduate and postgraduate students in the areas of medical biophysics. This Work is indispensable to all serious readers in this interdisciplinary area where physics is applied in medicine and biology. Written by leading scientists who have evaluated and summarized the most important methods, principles, technologies and data within the field, Comprehensive Biomedical Physics is a vital addition to the reference libraries of those working within the areas of medical imaging, radiation sources, detectors, biology, safety and therapy, physiology, and pharmacology as well as in the treatment of different clinical conditions and bioinformatics. This Work will be valuable to students working in all aspect of medical biophysics, including medical imaging and biomedical radiation science and therapy, physiology, pharmacology and treatment of clinical conditions and bioinformatics. The most comprehensive work on biomedical physics ever published Covers one of the fastest growing areas in the physical sciences, including interdisciplinary areas ranging from advanced nuclear physics and quantum mechanics through mathematics to molecular biology and medicine Contains 1800 illustrations, all in full color

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