THE MODERN TECHNOLOGY OF RADIATION ONCOLOGY: A Compendium for Medical Physicists and Radiation Oncologists. Volume 4

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***Abstract*— The technology of radiation oncology is evolving at an unprecedented rate. The challenge for medical physicists and radiation oncologists is to stay "au courant" with these rapidly changing advances that provide a better quality of life for cancer patients. The goal of *The Modern Technology of Radiation Oncology* is to provide state-of-the-art updated information on making these technologies available in the clinic. These volumes have not only been valued by medical and physics practitioners, but have also been appreciated by medical physicists and radiation oncologists who are in their residency training or in early years of practice, in addition to being a useful, single source compendium in preparation for certification exams. At the invitation of the co-editor of Medical Physics International, this paper provides a summary of the latest technological advances in radiation oncology as contained in *Volume 4* of *The Modern Technology of Radiation Oncology.* In addition to a brief historical review of the previous volumes, the following topics are summarized:**

- **Surface-guided radiation therapy (SGRT),**
- **Hybrid PET/MRI in radiation oncology,**
- **Real-time image guidance with magnetic resonance imaging,**
- **Stereotactic body radiotherapy**
- **Robust optimization and evaluation of radiation treatment uncertainties,**
- **Automated treatment planning,**
- **Artificial intelligence in radiation oncology,**
- **Adaptive radiation therapy,**
- **Machine learning in radiation oncology,**
- **Applications of big data in radiation oncology,**
- **Quantitative radiomics in radiation oncology,**
- **Radiobiological updates in particle therapy,**
- **High atomic number nanoparticle applications in radiation oncology,**
- **Financial and economic considerations in radiation oncology,**
- **Global considerations in the practice of medical physics,**
- **Emerging technologies for improving access to radiation therapy, and**
- **FLASH radiation therapy**

The intent of this book is that it will continue to provide guidance on the cost-effective and safe implementation of these new technologies into clinical practice with the ultimate aim of improving the quality of life of cancer patients.

Keywords— **Technology, radiation oncology, acceptance, commissioning, quality assurance.**

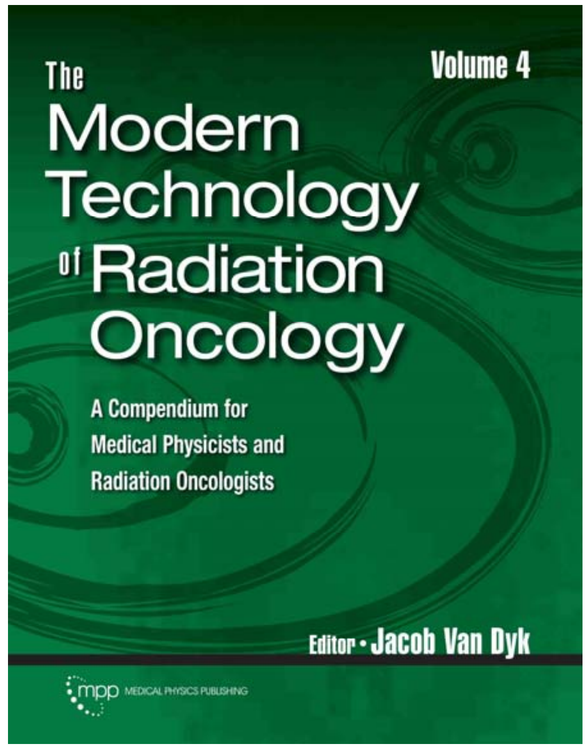

Figure 1. The front cover of *The Modern Technology of Radiation Oncology* published by Medical Physics Publishing in September 2020 [52].

I. INTRODUCTION

This paper is in response to an invitation by Perry Sprawls, the co-editor of Medical Physics International, in which he asked if I would consider writing an article presenting the new edition of T*he Modern Technology of Radiation Oncology. Volume 4* (Figure 1) [52] to the international medical physics community "with the purpose being to introduce this edition and emphasize the advances that are the major reason for this new publication." As he indicated, this is not a traditional book review but rather an article "briefly describing some of the advances and the new edition as the source of complete information and its value to the international medical physics community." I am delighted to provide this review in response to his invitation.

By way of background, it is helpful to understand a bit of the history of the previous volumes of the *Modern Technology of Radiation Oncology.*

Medical Physics Publishing (MPP) is a not-for-profit publisher, originally founded in 1985 by the renowned medical physicist, John Cameron, of the University of Wisconsin [25], In 1997, MPP approached me with an invitation to consider producing a book addressing issues related to the implementation of radiation therapy technologies into clinical practice. This invitation was instigated by Dr. Tomas Kron from Australia who upon request for ideas for new books had suggested this topic and me as a possible editor. The result was the first volume of *The Modern Technology of Radiation Oncology: A Compendium for Medical Physicists and Radiation Oncologists*, which was published in 1999 [49]. To quote from the preface,

> "**The purpose of this book is to describe the details of the technology associated with radiation oncology.** A special emphasis is placed on the **design** of all the equipment allied with radiation treatment. In addition, this book describes the procedures that are required to implement this equipment into clinical service (**needs assessment, purchase, acceptance, and commissioning**) and, once it is in use, the **quality assurance** that is required to keep the equipment operational at acceptable levels. In addition to describing all the tools that are used in "standard" radiation treatment centers, **this book addresses the less common or evolving technologies** and, thus, provides a comprehensive overview. Anyone embarking on any of these new procedures will be able to gain some basic insight as to what is required to make that procedure clinically viable."

The book consisted of 25 chapters and 1072 pages produced by 56 authors and co-authors, representing five countries, mostly the United States and Canada.

A few years after the publication of this book, the publisher asked me to consider a second edition. My reaction was that the contents in the original book and their applications had not changed substantially; however, in the previous five years, there were significant advances in ***new*** technologies associated with radiation oncology both in terms of hardware and software. These advances were attributed to innovations associated with oncological imaging, automated optimization of 3-D dose distributions, computer-controlled treatment delivery, and image-guided treatment. Thus, instead of producing a second edition, Volume 2 was developed "**to describe the significant incremental advances that have occurred with the technology associated with radiation oncology over the past 5 years.**" [50] Volume 2 was published in 2005 and consisted of 10 chapters and 466 pages produced by 22 authors and co-authors, representing three countries, again primarily from the United States and Canada.

Due to the advancements of new technologies in radiation oncology, primarily related to intensity-modulated radiation therapy, image-guided radiation therapy, adaptive radiation therapy, radiation therapy with light ions, and robotic radiation therapy, Volume 3 was published in 2013 [51]. In addition to the technological advances, other areas of increasing interest were also considered including quality assurance in the modern era, accuracy considerations in radiation oncology, growing concerns over patient safety and medical errors, staffing and resource issues, ethics, and medical physics considerations in clinical trials. The last chapter entitled *Radiation Oncology Medical Physics Resources for Working, Teaching, and Learning* provides a summary of useful resources for medical physicists working in the clinic, for medical physicists involved in teaching, and for medical physicists in training either at the graduate student or resident level. This chapter is a "live" chapter in that it is available on the Medical Physics Publishing website [48] and updated on a semi-regular basis approximately once per year.

Volume 3 consisted of 16 chapters and 574 pages produced by 34 authors and co-authors, representing five countries.

Figure 2 shows a graph of the number of books of the first three volumes sold per year over the 21 years that these books have been produced. The total books delivered by September 2020 was about 3500 books. eBooks of all three volumes were first made available in 2014, although eBooks sales are still in a minority with major preference still being given to hard copies. Records of purchases from specific countries did not start until 2018. While sales have always gone throughout the world, recent records include countries or regions such as China, Taiwan, Italy, Spain, United Kingdom and Oceania.

II. VOLUME 4

In late 2018 and early 2019, I was invited to give a couple of talks at joint international radiation oncology and medical physics conferences on the topic of future trends in the technology of radiation oncology. The preparation for these talks instigated some reflection on what had progressed in the technological evolution of radiation therapy in the last 5 to 10 years. In performing this review, it was clear that there were so many new advances in progress that it seemed important to produce another volume of *The Modern Technology of Radiation Oncology*. While not everything new started in the last 5

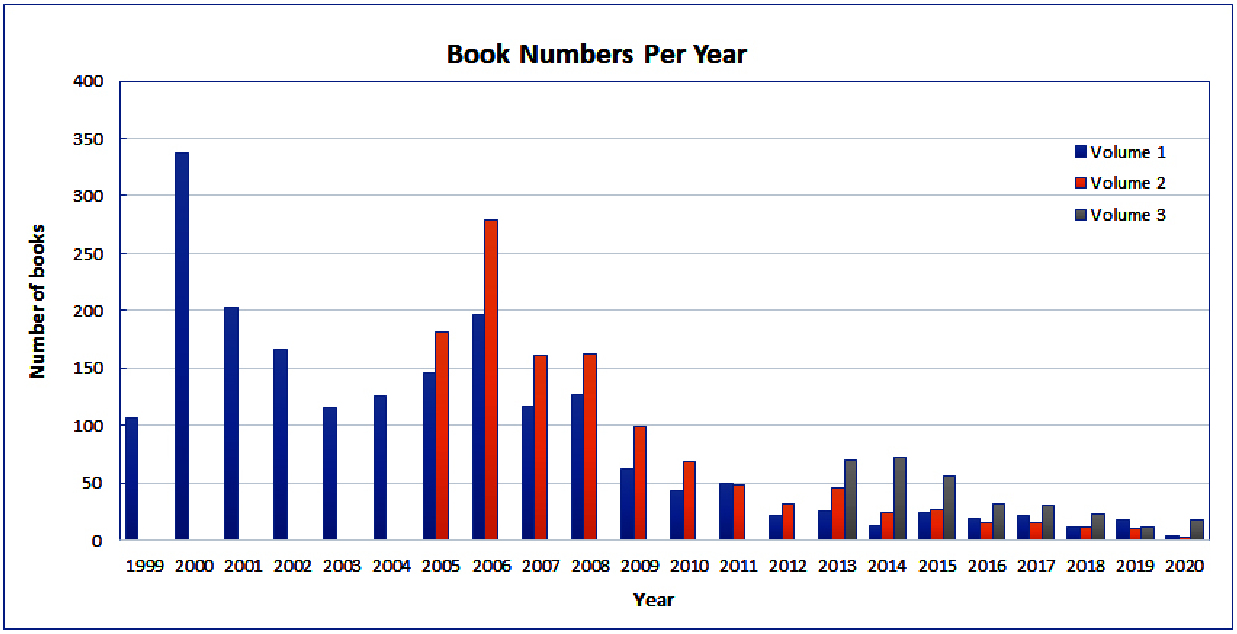

Figure 2. Number of books sold per year for the three volumes of *The Modern Technology of Radiation Oncology* since the publication of the first volume in 1999.

to 10 years, significant developments are presently in the process of being implemented in the clinical environment. Topics contained within Volume 4 include:

- Surface-guided radiation therapy (SGRT),
- Hybrid PET/MRI in radiation oncology,
- Real-time image guidance with magnetic resonance imaging,
- Stereotactic body radiotherapy
- Robust optimization and evaluation of radiation treatment uncertainties,
- Automated treatment planning,
- Artificial intelligence in radiation oncology,
- Adaptive radiation therapy,
- Machine learning in radiation oncology,
- Applications of big data in radiation oncology,
- Quantitative radiomics in radiation oncology,
- Radiobiological updates in particle therapy,
- High atomic number nanoparticle applications in radiation oncology,
- Financial and economic considerations in radiation oncology,
- Global considerations in the practice of medical physics,
- Emerging technologies for improving access to radiation therapy, and
- FLASH radiation therapy

Volume 4 was published in September 2020 and consists of 18 chapters and 524 pages printed in full color produced by 78 authors and co-authors, representing 11 countries [52]. This is the greatest international representation of all four volumes with nearly 40% of the authors being from countries other than Canada or the United States.

The following provides a very brief overview of the topics in each of the chapters in Volume 4. Some of these summaries are partially extracted from Chapter 1, which is available on-line [46].

Chapter 1. ***Technology Evolution in Radiation Oncology: The Rapid Pace Continues*** by J. Van Dyk

This chapter begins with a review of the technological evolution of radiation therapy since the discovery of x-rays in 1895 and addresses the question as to whether new technologies make a difference. While clinical benefits as a result of the introduction of new technologies are difficult to quantify in view of the multiple variables that are changing at the same, data from the 1970s and the 2010s demonstrate significant quantitative improvements in clinical outcomes, which can, at least in part, be attributed to the improvements in treatment technologies. The chapter goes on to provide a high-level summary of the subsequent chapters in the book. For several of the new technologies, annual journal publication rates are shown demonstrating that many of the topics are very recent areas of research and development.

One of the significant contributors to the improvements in radiation treatment technologies is the evolution of computer technology. Nearly all the steps in the radiation treatment process involve computer applications from diagnostic imaging, to surface or other guidance for patient set-up, to imaging for treatment planning, to the generation of an optimal treatment plan, to data transfer and automated treatment delivery along with image-guidance of the treatment set-up. All these computer-related procedures aim for the reduction of treatment margins to minimize normal tissue complications and allow for the escalation of tumor doses.

The chapter closes out with some predicted trends in radiation oncology including:

- More hybrid technologies,
- More automation,
- Turnkey installations,
- Reduced use of planning target volumes,
- Increased emphasis on cost considerations,
- Increased regulatory oversight,
- Increased use of particle therapy,
- Increased use of radiobiological models in treatment planning,
- Further development of radiomics applications, and
- Clinical implementation of FLASH therapy.

The chapter summary indicates that perhaps the title should have been *Technology Evolution in Radiation Oncology: The Rapid Pace Escalates* since the rate of change is significantly more rapid now than at the time of the previous volumes.

Chapter 2. ***Surface Guidance in Radiation Therapy*** *by* Hania A. Al-Hallaq, Alonso N. Gutierrez, and Laura I. Cerviño

While surface guidance technologies have been under development already since the 1970s, it is only during the last decade that these have become more routinely and commercially available. Surface-guided radiation therapy (SGRT) involves the use of real-time patient position data before and during simulation with imaging modalities such as CT, MR and PET, and for radiation treatment delivery on the treatment machine. This also includes positioning for respiratory-correlated procedures. SGRT uses sophisticated 3-D camera technologies to track the patient's skin surface; hence, its ability not only to position the patient accurately and reproducibly but also allow for motion management. It provides a positioning accuracy of better than 1 mm and can detect rotational offsets of less than 1 degree. Developments under consideration include collision detection and biometric measurements. In view of the non-ionizing nature of this 3-D imaging modality, it enables the collection of vast amounts of real-time data about patient treatments that is expected to benefit the field in novel ways in the future. It is only in the last 2 years (2018-2019) that publications on the use of SBRT have started to appear more frequently, with 53% appearing in those years compared to the total number of publications since 1975.

Chapter 3. ***PET/MRI as a Tool in Radiation Oncology*** by Jonathan D. Thiessen, Stewart Gaede, and Glenn Bauman

PET/MRI is a hybrid imaging technology that incorporates MRI soft tissue morphological imaging and PET functional imaging providing information on metabolic activity. While this hybrid technology has been in a developmental stage already since 1997 [26], it was first introduced commercially in 2011. One recent study compared PET/MRI to PET/CT in whole body oncological imaging for lesion detection and classification using 1003 examinations [23]. Their conclusions were that PET/MRI improves lesion detection and potentially reduces additional examinations in tumor staging, and especially younger patients may benefit from the clinically relevant dose reduction of PET/MRI compared to PET/CT. However, the significant cost of whole-body PET/MRI (approximately double that of a standalone 3T MRI or PET/CT systems with similar specifications) has limited its implementation in the clinic. With further advancements in technology, future PET/MRI systems may target a more affordable price point.

Chapter 4. ***Real-Time Image Guidance with Magnetic Resonance*** by Jan J. W. Lagendijk, Bas W. Raaymakers, Rob H. N. Tijssen, and Bram van Asselen

Image-guided radiation therapy using 3-D CT imaging has been in the clinic since the early 2000s. Helical tomotherapy was already described in detail in Volume 1 in 1999 [29]. Since then cone-beam CT (CBCT) has been implemented for IGRT on conventional linacs [18]. The CT imaging on both technologies is usually done prior to treatment. Upon review of the images, the patient is repositioned and treated. The total process of imaging and review may take several minutes. These systems cannot provide any *real-time* feedback during the actual treatment to see if there is any change in position while the beam is on. More recently, the combination of a linear accelerator (linac) with an MR scanner has become available clinically and provides real-time imaging while the treatment beam is on. Thus, the radiation oncologist can see if there is a change in tumor volume and surrounding structures daily and determine if the treatment plan needs to be adapted to the modified anatomical shape. Also, the real-time images will allow tracking of the tumor position during treatment with the possibility of the beam position being adjusted to follow the motion of the tumor, especially for cases such as lung tumors, where there is significant breathing motion during the treatment.

To quote from the conclusions, "The "blue sky" will be real-time adaptive radiotherapy where the dose delivery is continuously being optimized during the actual delivery using the continuous stream of imaging data, making radiotherapy a robotic interventional procedure [22]. The extreme targeting accuracy will facilitate the use of dose painting, but consequently will require knowledge on tumor characterization and delineation. A close collaboration between the radiation oncologist, radiologist, pathologist, and medical physicist is needed. Online MRI also provides capabilities of tumor characterization and tumor response assessment in the actual treatment optimization.

Online MRI guidance may start a paradigm shift in radiotherapy: the central position becomes MRI-guided targeting and its related tumor delineation and characterization."

Chapter 5. ***Stereotactic Body Radiotherapy*** by Mischa S. Hoogeman, Patrick V. Granton, Maaike T. W. Milder, Ben J. M. Heijmen, and Hanbo Chen

Stereotactic body radiotherapy (SBRT) has become a clinical standard of practice in nearly every modern radiation therapy department. SBRT delivers a precise, high doses of radiation to the tumor especially for tumors in the lung, prostate, pancreas, liver, spine, and kidney while minimizing damage to the surrounding normal, healthy tissues. It allows for high doses per fraction and relatively fewer fractions. For non-small cell lung cancer (NSCLC), the preponderance of evidence suggests that SBRT is associated with excellent local control (~90% at 3 years) and a favorable toxicity profile [6]. In patients with higher operative risks, such as the elderly and patients with severe chronic obstructive pulmonary disease, SBRT may provide a less-toxic treatment than surgery with similar oncologic outcomes. Ongoing studies are evaluating the use of SBRT for locally advanced or oligometastatic NSCLC.

Chapter 6. ***Radiation Treatment Uncertainties: Robust Evaluation and Optimization*** by Roel G. J. Kierkels, Albin Fredriksson, and Jan Unkelbach

Giving the highest dose possible to the tumor while constraining normal tissue doses to acceptable levels are two of the main considerations in developing an optimized treatment plan. However, it is now well recognized that treatment uncertainties can vary dramatically dependent on the nature of the treatment plan in terms treatment technique and the technology used. The concept of *robust optimization* has been under consideration for a number of years. In 1997, our group began addressing issues related to uncertainties and their impact on developing optimized treatment plans [56]. The field has advanced to robust optimization whereby plans are calculated and optimized in such a way that they are minimally affected by uncertainties. Robust optimization is now available on commercial treatment planning systems. In reviewing the number of publications per year on robust planning in radiotherapy, nearly 50% occurred in the last 5 years. Robust planning has become especially relevant for particle therapy where range uncertainties can have dramatic effects on dose delivery both to the target and the normal tissues. This has led to probabilistic estimations of dose distributions. These distributions can now be calculated and could possibly replace the planning target volume (PTV) concept since the generation of the clinical target volume (CTV) to the PTV margin is performed based on the uncertainty distributions [44]. Our group already proposed the direct calculation of treatment plans without using the PTV concept in 2001 [7].

Chapter 7. ***Automated Treatment Planning*** by Laurence Court, Carlos Cardenas, and Lifei Zhang

The entire radiation treatment process has multiple steps. With the recent rapid advancements in computer technology and the development of improved and faster optimization algorithms, the calculation component of generating a treatment plan has improved significantly. In addition, auto-segmentation for tumor and normal tissue delineation allows the time taken by the radiation oncologist and the treatment planner to be reduced significantly. Many treatment planning systems now provide scripting capabilities where it is possible to record a sequence of messages or keystrokes while the user is operating the system. Scripts can be used within the radiation treatment planning system to reduce human error, to increase treatment planning efficiency, to reduce confusion, and to promote consistency within an institution or even among different institutions [16]. Scripting has been used for automated IMRT planning both for simple cases such as localized prostate and whole breast cancers [33] as well as more complex cases such as head and neck, anal canal and prostate with pelvic nodes [57]. Xhaferllari et al [57] make a comparison between the time to generate a manual plan versus the time to generate an automated plan. Their results demonstrate a huge time savings by automation (up to factors of 30). In addition, because of the self-consistency of the scripting process, the scripts can reduce variations of plan quality due to the differences in experience of the planners.

Software for auto-contouring of images and automatic generation of treatment plans is becoming more readily available on commercial treatment planning systems. Furthermore, their speed is increasing such that they allow for on-line adaptation of the treatment during every treatment fraction. A critical step is the validation and clinical approval of the auto-segmentation and automatically generated treatment plans by radiation oncologists and medical physicists. To reach the goal of on-line biological image-guided adaptive radiation therapy, this validation and approval needs to be streamlined so that it can be done in a few minutes rather than in hours [12]. As pointed out in this chapter, the type of software that supports automation of the contouring and treatment planning process is especially useful in lower income contexts since it provides the potential for scaling up radiation therapy capacity to meet global needs.

Chapter 8. ***Artificial Intelligence in Radiation Oncology*** by Tomi Nano, Matthieu Lafrenière, Benjamin Ziemer, Alon Witztum, Jorge Barrios, Taman Upadhaya, Martin Vallières, Yannet Interian, Gilmer Valdes, and Olivier Morin

Artificial intelligence (AI) is the simulation of human intelligence processes by machines, especially computer systems [39]. Specific applications of AI include expert systems, natural language processing (NLP), speech recognition and machine vision. AI programming focuses on three cognitive skills: learning, reasoning and self-correction. The **learning process** aspect of AI programming focuses on acquiring data and creating rules for how to turn the data into actionable information. The rules (algorithms) provide computing devices with step-by-step instructions for how to complete a specific task. The **reasoning process** focuses on choosing the right algorithm to reach a desired outcome. The **self-correction process** is designed to continually fine-tune algorithms and ensure they provide the best results possible.

The annual publication rate for “artificial intelligence in radiation oncology” demonstrates a clear dramatic growth in the last few years with 50% of all publications occurring between 2016 and 2019.

The applications in the context of radiation oncology are numerous including, for example, automated treatment planning, auto-segmentation, image processing and QA activities [8;54]. Applications of AI to improve the quality and safety in radiation therapy are also in progress [32].

By way of their conclusion, a long-term hypothesis is that AI development in radiation oncology will provide solutions that are able to create real-time, patient-specific knowledge which will save lives and reduce side effects.

Chapter 9. ***Adaptive Radiation Therapy (ART)*** by Emily A. Hewson, Doan T. Nguyen, Geoffrey D. Hugo, Jeremy T. Booth, and Paul J. Keall

While ART was first described in 1997 by Di Yan [58], the onset of multiple publications per year started in about 2005. This chapter addresses ART directly although aspects of ART are also discussed several other chapters.

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Biologically adapted radiotherapy can be considered as the most advanced form of ART, since it involves functional imaging to extract biological tumor surrogates or features, and thus needs a multidisciplinary approach. Thorwarth illustrates the complexity by discussing the whole development chain of biologically ART from radiobiologically relevant processes, to functional imaging techniques which visualize tumor biology non-invasively, to the implementation of biologically adapted radiation therapy in clinical practice [41]. It is clear that ART will be a main contributor to the radiation oncology process with geometric and anatomical adaption being available and biological adaption evolving such that it becomes a true contributor to personalized medicine.

Chapter 10. ***Machine learning in Radiation Oncology: What Have We Learned So Far?*** by Issam El Naqa, Jean M. Moran, and Randall K. Ten Haken

As a significant component of AI, machine learning is the development of data-driven algorithms that learn to mimic human behavior based on prior example or experience [19]. The recent rapid increase on machine learning publications shows that 70% of them occurred in 2018 and 2019.

Applications of machine learning [19] include improvements in low-dose imaging for therapy planning, the use of MRI for the generation of CT-like electron densities for treatment planning [10;11;24], multimodal image fusion for radiation therapy planning [5;21], image segmentation for tumor and normal tissue delineation [36], treatment planning, plan approval and QA [37;42], and, finally, dose delivery and treatment adaptation [43]. Significant components of the treatment process have had considerable research in the context of machine learning and the corresponding challenges. One of the main challenges is knowing the ground truth. Learning-based models are only as good as their training data. Machine learning is evolving rapidly and is an excellent means of providing consistency and efficiency facilitating both transfer of best practice between physicians and clinics and greater process automation.

Chapter 11. ***Applications of “Big Data” in Radiation Oncology*** by Biche Osong, Andre Dekker, and Johan van Soest

The radiation therapy process is complex consisting of multiple steps. The new advances in technology allow enormous amounts of data to be generated for each patient during their total treatment process. The comparison is like a snowball rolling down a hill. It is the accumulation of these data for each step in the process for which the radiation oncologists need help for translation into knowledge that supports decision-making in their clinical practice.

The research analysis of these large amounts of data relies on analytical methods from the emerging science of "big data" informatics. This "big data" refers to extremely complex datasets characterized by the four Vs: *volume*, which refers to the sheer number of data elements within these extremely large datasets; *variety*, which describes the aggregation of data from multiple sources; *velocity*, which refers to the high speed at which data is generated; and *veracity*, which describes the inherent uncertainty in some data elements [20].

In summary, the promise of big data in radiation oncology is to provide improved access to the collective experience of treating patients to improve care for new and future patients. This improvement can take the form of actions such as reducing geographic disparities in care; ensuring continual quality improvement for individual practices; and ideally, personalizing treatments based on the outcomes of prior, similar patients. Each of these objectives requires different levels and resolution of clinical data that may be contained in registries, electronic medical records, tissue banks, and treatment planning and imaging systems [3].

Chapter 12. ***Quantitative Radiomics in Radiation Oncology*** by Mattea L. Welch, Alberto Traverso, Caroline Chung, and David A. Jaffray

A very recent, new field of study in radiation oncology and diagnostic imaging is known as *radiomics*. The first publications on "radiomics occurred in 2012 and since then over 70% of the publications occurred in 2018 and 2019 indicating an extremely rapidly increasing area of research. Radiomics is based on the extraction of a large variety of features from medical images using data-driven algorithms to characterize tumors [35]. The image data are further processed with a variety of reconstruction algorithms to obtain images that generate tumor-characteristic features. Automatic image segmentation is used to generate appropriate volumes of interest.

Radiomics has the potential for providing guidance on a number of applications in radiation oncology including [55]: (1) prediction of clinical outcomes [27;28]; (2) prognostication [17]; (3) prediction of the risk of distant metastases [45]; (4) assessment of cancer genetics [13;14]; (5) tumor dynamics changes through data generated by IGRT [59]; (6) distinguishing tumor progression from radionecrosis [31]; (7) prediction of physiological events with, e.g., the use of functional MRI [15]; and (8) the use of multiparametric radiomics for detection, characterization and diagnosis of various diseases including breast cancer [30].

The use of radiomics overlaps with applications of AI, machine learning and big data. Machine learning algorithms of AI boost the powers of radiomics for the prediction of prognoses or factors associated with treatment strategies, such as survival time, recurrence, adverse events, and subtypes. Radiomic approaches, in combination with AI, may potentially enable practical use of precision medicine in radiation therapy by predicting outcomes and toxicity for individual patients [1].

Chapter 13. ***Radiobiological Updates in Particle Therapy*** by Harald Paganetti and Michael Scholz

In the early years (1950-1970s), proton therapy was only available in very few institutions that had access to high energy particle facilities that were primarily used for physics research purposes. More recently, accelerator technology has been designed very specifically for clinical radiation therapy applications for both protons and heavier particles and the number of hospital-based clinical facilities is escalating rapidly. Furthermore, new advanced capabilities, such as beam scanning, IMRT, IGRT, along with robust treatment planning are providing further advances beyond the tight dose distributions provided by particle treatment. While the majority are proton centers, there are also some dedicated carbon ion facilities, as well as several facilities with the capability to treat with either [9]. Of the number of publications per year on protons and heavier particle radiation therapy since 1954, about 50% were published between 2014 and 2019.

Generally, it has been assumed that the relative biological effectiveness (RBE) for protons is a constant 1.1 over the entire irradiated volume. However, as pointed out in this chapter, RBE values are probably higher at the end of the proton range, potentially affecting normal tissue toxicities, although the RBE variations are likely smaller than the variability in patient radiosensitivity. For heavier particles, however, the change in RBE values are significantly larger and need to be considered as a function of particle species, particle energy, depth of penetration and type of tissue. It appears that current models, while not mechanistic, seem to be sufficiently accurate for clinical treatment planning purposes.

Chapter 14. ***Radiation Oncology using Nanoparticles with High Atomic Numbers*** by Romy Mueller, Jana Wood, Mohammed Jermoumi, Ysaac Zegeye, Sayeda Yasmin-Karim, Kaylie DeCosmo, Michele Moreau, Francis Boateng, Juergen Hesser, and Wilfred Ngwa

Nanotechnology relates to the manipulation of matter on atomic or molecular scales, generally less than 100 nanometers. The use of nanotechnology in medicine has led to what is now known as *theranostics*, where theranostics involves using nanoscience to unite diagnostic and therapeutic applications to form a single agent, allowing for diagnosis, drug or dose delivery and treatment response monitoring. Nanomaterials have several characteristics that are relevant for oncology applications, including preferential accumulation in tumors, low distribution in normal tissues, and biodistribution, pharmacokinetics, and clearance, that differ from those of small molecules. Because these properties are also well suited for applications in radiation oncology, nanomaterials have been used in many different areas of radiation oncology for imaging and treatment planning, as well as for radiosensitization to improve the therapeutic ratio [34;53]. Nanoparticles have been engineered from a wide range of materials that can be divided into inorganic and organic nanoparticles. One unique strategy is to increase the effect of the external beam radiation dose within tumor tissue by using materials with high atomic numbers (Z). This is because the dose absorbed by any tissue is related to some power of Z of the material depending on the energy. If an agent can increase the overall effective Z of the tumor without affecting the Z of nearby normal tissue, it can lead to increased radiotherapy dose to tumors and higher therapeutic efficacy.

This review summarizes the current status of research and development toward the use of high-Z nanoparticles to enhance radiation therapy. Considerations addressed nanoparticle design, delivery, as well as radiotherapy beam and treatment planning factors. Various innovative developments were addressed as a part of the outlook.

Chapter 15. ***Financial and Economic Considerations in Radiation Oncology*** by Yolande Lievens, Danielle Rodin, and Ajay Aggarwal

While the increasing complexity of the modern technology of radiation oncology has demonstrated improvements in patient outcomes, this comes at a considerable cost. Much emphasis has been placed in recent years on the financial and economic considerations in radiation oncology. Furthermore, there has been significant discussion in the recent literature on the global needs of radiation oncology along with the estimated overall costs according to national income levels [2;47;60]. This chapter provides detailed guidance on economic considerations. One of the issues that arises out of these discussions goes beyond the dollar cost analysis and has been described as assessing *value* per dollar spent. The discussion on *value* is complex. The definition of value will vary depending on several factors, including the social identity and the social context of the person purchasing the product or service [40]. The desirable product or service as well as the fair price is in the eye of the beholder. Teckie et al go on to describe their interpretation of *value* in healthcare [40]. Where value has been described as outcomes/cost, they suggest it should be expanded to include structure and process; thus, transforming the value equation to value equals quality/cost. The key components of value include structure, process, outcomes and costs. This type of value-based approach requires more involvement of the patient and adds another component to what has become known as personalized medicine.

The chapter summary indicates that in an era of restricted healthcare budgets, the need for knowledge on the cost and economic aspects of existing and novel interventions has increased.

Chapter 16. ***Global Considerations for the Practice of Medical Physics in Radiation Oncology*** by Jacob Van Dyk, David Jaffray, and Robert Jeraj

This chapter on global considerations in radiation oncology medical physics provides a worldwide perspective of medical physics, addressing questions such as: what is the status of medical physics around the world, how are medical physicists trained, what are the issues, what are the solutions, etc. For example, as pointed out by the Global Task Force on Radiotherapy for Cancer Control (GTFRCC) [2], it is clear that there is a huge disparity of the availability of medical physicists by country, dependent on the country's income level as described by the gross national product.

Many scientific and professional organizations, also those related to Medical Physics, provide various levels of support to international outreach activities for individuals from LMICs via reduced membership fees, special travel grants, other specific awards, as well as in the realm of providing education and training. Indeed, many of these organizations are increasing their outreach efforts. It is clear that future demand for medical physics research and clinical support around the world requires multipronged approaches with the global community working together.

In summary, this chapter has addressed a number of issues related to global considerations in radiation oncology medical physics, ranging from variations in education and training (along with the corresponding credentialing) to addressing global disparities that are not only manifested in LMIC contexts, but also exist in HIC contexts. Models for addressing global physics education are reviewed, along with a discussion on issues to contemplate in addressing global disparities and the corresponding considerations in international outreach. These issues and their solutions are not simple; however, this chapter has attempted to provide some food for thought on factors to consider in this context.

Chapter 17. ***Emerging Technologies for Improving Access to Radiation Therapy*** by Holger Wirtz, Ralf Müller-Polyzou, Anke Engbert, Rebecca Bücker, Godfrey Azangwe, Tomas Kron, Marian Petrovic, Mahmudul Hasan, and Ernest Okonkwo

The report by the GTFRCC [2] as well as others make it very clear that there is a need for additional radiation therapy equipment as the burden of cancer escalates, especially in LMICs. Filling the gap in cancer care in underserved regions worldwide requires global collaboration and concerted effort to share creative ideas, pool talents and develop sustainable support from governments, industry, academia and non-governmental organizations. To build capacity with high quality capability and with the credibility to conduct research to understand specific diseases and treatment outcomes requires a complex systems approach toward both expertise and technology. This chapter addresses some of these issues in detail.

Chapter 18. ***"FLASH" Radiation Therapy: A New Treatment Paradigm*** by Peter G. Maxim, Billy W. Loo, Jr., Claude Bailat, Pierre Montay-Gruel, Charles L. Limoli, and Marie-Catherine Vozenin

Recent research delivering radiation doses at ultrahigh dose rates, roughly 50 Gy/s and above, could vastly reduce normal tissue toxicity while preserving anti-tumor activity [38]. So far, the evidence is growing in laboratory experiments. If the evidence is maintained in human clinical trials, this has the potential of being one of the very significant breakthroughs in radiation therapy of recent times [4]. Details of FLASH radiation therapy are discussed in this chapter. Based on their summary, FLASH promises to be a paradigm shift in curative radiation therapy with preclinical evidence of fundamentally improved therapeutic index. While much remains to be learned about the mechanisms underlying the phenomenon, technological developments are in place for both short-term clinical implementation of FLASH radiation therapy for limited clinical scenarios and longer-term application for more general cancer indications. Selective early clinical testing of FLASH will provide unique opportunities for elucidating its biological mechanisms in human patients through the collection and analysis of biosamples, the understanding of which will ultimately be needed for optimal clinical application of FLASH radiation therapy.

III. SUMMARY

The Modern Technology of Radiation Oncology of Radiation Oncology: A Compendium for Medical Physicists and Radiation Oncologists. Volume 4 consists of a compilation of recent technological advances in addition to related considerations. It is clear that the technological changes have increased at unprecedented rates. The challenge for medical physicists and radiation oncologists is to stay "au courant" with these rapidly changing advances that provide a better quality of life for patients. These volumes have not only been valued by clinical and physics practitioners, but also have been appreciated by medical physicists and radiation oncologists who are in their residency training or in early years of practice, in addition to being a useful resource compendium in preparation for certification exams. My hope remains that this series of books will continue to provide guidance on the cost-effective and safe implementation of these technologies into clinical practice with the ultimate aim of improving the quality of life of cancer patients.

ACKNOWLEDGMENT

A sincere thank you:

- To the *authors and co-authors of the chapters* of this series of books. They have given much of their time and knowledge to make these the quality books they are. Without their contributions, these books would not exist.
- To *Todd Hanson and the staff at Medical Physics Publishing* for detailed editing support of Volume 4 and for bringing this work to a timely completion.

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