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The physical basis and future of radiation therapy

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ABSTRACT. The remarkable progress in radiation therapy over the last century has been largely due to our ability to more effectively focus and deliver radiation to the tumour target volume. Physics discoveries and technology inventions have been an important driving force behind this progress. However, there is still plenty of room left for future improvements through physics, for example image guidance and four-dimensional motion management and particle therapy, as well as increased efficiency of more compact and cheaper technologies. Bigger challenges lie ahead of physicists in radiation therapy beyond the dose localisation problem, for example in the areas of biological target definition, improved modelling for normal tissues and tumours, advanced multicriteria and robust optimisation, and continuous incorporation of advanced technologies such as molecular imaging. The success of physics in radiation therapy has been based on the continued “fuelling” of the field with new discoveries and inventions from physics research. A key to the success has been the application of the rigorous scientific method. In spite of the importance of physics research for radiation therapy, too few physicists are currently involved in cutting-edge research. The increased emphasis on more “professionalism” in medical physics will tip the situation even more off balance. To prevent this from happening, we argue that medical physics needs more research positions, and more and better academic programmes. Only with more emphasis on medical physics research will the future of radiation therapy and other physics-related medical specialties look as bright as the past, and medical physics will maintain a status as one of the most exciting fields of applied physics.

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Radiation therapy would not exist without physics. This obvious but sometimes forgotten fact is the guiding principle of this review article. While radiation therapy “lives” at the interface between many disciplines, its dependence on physics is arguably the strongest. By this we mean not only the dependence on clinical physics support to make sure that radiation is being administered safely and accurately, but primarily the dependence on the science and research side of physics in general and medical physics in particular. We tend to think of medical physics as physics in medicine, to emphasise the importance of physics. One question that we will try to answer is: what is the recipe for success of physics in medicine? In Part 1 we will first identify the traditional contributions of physics in radiation therapy mostly focused on the physics of precise radiation “dose localisation”. Throughout this article we define dose localisation as the ability to deliver dose precisely and accurately to a region of interest in the patient (*i.e.* the tumour target volume). This clearly comprises not only advancements in delivery technology but also in treatment planning and especially in imaging. We will then

look at physics contributions beyond dose localisation and even beyond radiation therapy. In Part 2 we will discuss the role of physicists in radiation therapy and the challenges that we currently face, especially the diminishing emphasis on the research role. Lastly, we will provide some suggestions on how to address those challenges in the future to secure a sustainable environment for long-term and high-impact physics in medicine.

Part 1: dose localisation and beyond

What have we achieved so far?

The history of physics in radiation therapy begins with the discovery of X-rays by Wilhelm Conrad Röntgen in 1895. Of the many “gifts” that physics has made to medicine, the discovery of X-rays is probably the greatest. The enormous potential of X-rays not only for diagnostic imaging but also for the treatment of diseases was recognised soon after the discovery. The first patient treatment with X-rays occurred only 1 year after the discovery. Thus, a physics discovery launched the field of radiation therapy.

The main focus of physics in radiation therapy has always been to increase the level of precision and accuracy of dose delivery to the (tumour) target volume.

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Remarkable progress has been made in this area, which is based on four cornerstone developments:

1. Fundamental discoveries leading to new treatment and imaging modalities.
2. Technology inventions in radiation dose delivery.
3. Technology inventions in treatment planning.
4. Technology inventions in imaging.

Some of the most important milestones are listed in Table 1. While some of the applications of physics in radiation therapy originated in radiation oncology and were the result of goal driven research and development, many were the result of fundamental physics discoveries outside the field that found an application in radiation therapy.

Fundamental discoveries leading to new treatment modalities

While most of the fundamental discoveries were initially not intended for their use in medicine, it often did not take long before they were applied to medical problems. Interestingly, in some cases (X-rays, radioactivity) it took only a couple of years from discovery to the first application of this type of radiation as a new treatment modality in medicine. In other cases, specifically in proton therapy, it took 35 years from the

fundamental physics discovery until the first patient treatment. Medical physics is crucial for translating new treatment and imaging modalities in the clinic, and assuring that the radiation delivery is safe, reliable and efficient.

Technology inventions in radiation dose delivery

Among the main factors contributing to the remarkable accuracy and precision of dose localisation are advancements treatment delivery technology. In the most prevalent form of external photon beam radiation therapy, these include the development of treatment machines (specifically linear accelerators) with higher energies and better depth dose characteristics and skin sparing, as well as smaller sources for reduced lateral penumbra, which date back to the 1950s. They also include advanced field shaping devices (multileaf collimators) for three-dimensional conformal radiation therapy and intensity-modulated radiation therapy (IMRT) in the 1980s, with several earlier forerunners. Improved patient immobilisation techniques and motion management techniques also belong to this category. Development of dedicated treatment machines with greater geometric precision such as dedicated stereotactic machines, ring-gantry machines such as tomotherapy, as well as robotic treatment machines in the 1990s, push dose delivery even further.

Table 1. Physics milestone advancements in radiation therapy. Several Nobel Prize winning discoveries and inventions have “fuelled” the field of radiation therapy, others have affected radiation therapy more indirectly, such as positron emission tomography imaging enabled by the discovery of the positron (1936) and the coincidence method (1954)

Fundamental discoveries leading to new treatment and imaging modalities	
1895	Discovery of X-rays (Nobel Prize in physics for Röntgen in 1901) leading to X-ray (CT) imaging and first radiation treatment of cancer with X-rays only 1 year later
1896	Discovery of radioactivity (Nobel Prize in physics for Becquerel/Curie in 1903) leading to the first treatment with radioactive isotopes shortly thereafter [3]
1919	Discovery of the proton, leading to the first patient treatments with a proton beam in 1954
1938, 1946	Discovery of nuclear magnetic resonance (Nobel Prize in physics for Rabi in 1944 and Bloch and Purcell in 1952), leading to MRI in the 1970s
Technology inventions in radiation dose delivery	
1951	Cobalt-60 treatment machines become clinically available: use of high-energy gamma rays for better skin sparing
1953	Linear accelerators with higher energies for better skin sparing and improved penumbra [4]
1950s	Cyclotrons for proton therapy (physics Nobel Prize for Lawrence in 1939)
1986	Radiation field shaping with multileaf collimators [5]
1994	Intensity modulated radiation therapy (IMRT)
Technology inventions in treatment planning	
1960s	Use of computers for dose computation
1980s	Development of three-dimensional treatment planning
1987	Inverse treatment planning and plan optimisation techniques
Technology inventions in imaging	
1972	CT (Nobel Prize in Medicine for Cormack and Hounsfield in 1979), which is soon used for radiation treatment planning
1970s	MRI (Nobel Prize in Medicine for Lauterbur and Mansfield in 2003)
2000s	Imaging integrated into treatment machines for image guided radiation therapy

This table, like the accompanying list of references, is far from exhaustive and represents solely the subjective view of the authors. For a more in-depth review, the interested reader is referred to other excellent review articles and books that have been written on the history of physics in radiation therapy, and, more generally, on physics in medicine, particularly [1] and [2].

Technology inventions in treatment planning

Advanced methods of calculating the three-dimensional radiation dose distribution in the patient with great precision and optimising the dose distribution started when more powerful computers became available in the 1960s, and especially when affordable personal computers appeared in the 1970s. The ubiquitous availability of cheap and powerful computers in later years made it possible, even for relatively small medical physics groups, to develop algorithms for dose calculation (pencil beam and convolution/superposition algorithms, Monte Carlo), treatment planning (three- and four-dimensional) and optimisation ("inverse" treatment planning). In many cases, after proof of principle demonstration and initial testing, commercial companies took these software prototypes and basic concepts from the medical physicists and developed them into commercial products, which made them available to the broader community.

Technology inventions in imaging

Targeting the tumour with the "radiation scalpel" with great accuracy is clearly impossible unless we know the position and extension of the tumour in the patient in three-dimensions. This was first enabled by the development of CT in the 1960s and 1970s. CT is perhaps the most important breakthrough in radiation therapy after the discovery of X-rays. The series of reviews to which this article belongs is appropriately named after Sir Godfrey Hounsfield, an electrical engineer, the main driving force behind the development of CT [6] and joint winner of the 1979 Nobel Prize for CT with Dr Allan Cormack, a physicist. Interestingly, Dr Cormack's motivation to develop CT came from the desire to calculate the radiation dose in radiation therapy with greater accuracy, which required the attenuation coefficients of the tissues in the human body to be known in three-dimensions [7]. That such a device could then also lead to better diagnostic imaging was somewhat of

an afterthought for Dr Cormack. Other imaging inventions and developments, such as MRI and positron emission tomography (PET) imaging, also had an impact on radiation therapy, but not nearly as much as CT. An important developing area is image guided radiation therapy (IGRT). It typically refers to three-dimensional CT imaging during treatment process, which pushes imaging in radiation therapy beyond diagnostic application.

Overall, the history of physics in radiation therapy is one of improved dose localisation in space and time. The progress made in this area is indeed quite remarkable. The medical physics mantra of concentrating radiation dose to the tumour target volume and sparing surrounding healthy tissues as much as possible has been successful and has led to a dramatic difference in how we plan, optimise and deliver radiation therapy (Figure 1). Highly concentrated dose deliveries to the tumour within 1–2 mm spatial accuracy, and 2% dose accuracy, are now possible. The dose to healthy tissues has been substantially reduced by better geometric dose shaping and use of advanced treatment modalities, including proton and heavier particle therapy. Combining this with the radiobiological advantage of a differential capability for damage repair between tumour and normal tissues, we are now in a position of delivering radiation treatments that are able to clinically control the tumour at the same time as avoiding toxicity of normal tissues. None of this would have been possible without the phenomenal basic physics and technology development advances that we have witnessed in the last 100 years.

What is the recipe for success of physics?

Evolution and continued success of radiation therapy, since its inception more than a century ago, has been, in large part, due to technological advancements that lead

Figure 1. 100 years of development in radiation therapy have made a difference. Comparison of an X-ray treatment plan from the early 1900s ((a), from [8]) and a proton treatment plan from the early 2000s ((b), courtesy of AW Chan and AV Trofimov, MGH Boston).

to improvements of dose localisation. A good question to be asked is: what are those crucial contributions from physics to radiation therapy that could not have come from other disciplines?

Rigorous scientific methodology

Physicists employ a rigorous scientific method that is needed for fundamental discoveries and technology inventions. This review looks at a couple of examples of its application in radiation therapy, first the invention of CT (see [9] for a similar discussion). Both Hounsfield and Cormack tried to answer important questions: how to improve the sensitivity of X-ray imaging, and how to improve the precision of dose calculation in radiation therapy. Both took a step back to look at the bigger picture and realised that what was needed was the "reconstruction" of a cross-sectional image of the patient from measurements outside of the patient. Then they had an idea (the hypothesis) that this might be possible by taking X-ray "projections" from many different directions, and reconstructing the cross-sectional image with a calculation method (using a computer). Hounsfield then pursued a more experimental approach and Cormack pursued a more theoretical one. Both of them proved the hypothesis and along the way made an enormous impact in radiation therapy, and more generally in clinical medicine.

Another good example of the scientific method in radiation therapy physics is the invention of IMRT by Brahme et al [10] and forerunners [11]. It started with the clinical question: how to treat certain paraspinal tumours that bend around the spinal cord? This specific case led them to define an abstract problem of a ring-shaped target volume around a circular critical structure, which they could solve analytically using some simplifications. The solution required highly intensity modulated beams, as opposed to the standard treatment beams with uniform intensity. This then led them to hypothesise that intensity-modulated beams are beneficial in a more general way for the treatment of all complex and non-convex target volumes, and the idea of IMRT was born. In these examples, along with many more, a straight-forward technological approach would not have produced the solutions that turned out to be so useful in the clinic.

Interface between physics and medicine through physical quantities

An interface between physics and medicine can only be created on the basis of carefully chosen physical quantities. A major cornerstone of the success of radiation therapy is the definition of the physical quantity of absorbed radiation dose, *i.e.* the energy imparted per unit mass, measured in units of gray. The radiation dose can be measured quite easily in three-dimensions in simple geometric or anthropomorphic phantoms. It can be calculated with good accuracy in the patient using convolution/superposition or Monte Carlo methods. Therefore, to develop, test and validate new methods for improved dose localisation, physicists can use computer simulations in combination with phantom measurements and get an answer almost immediately. Involved clinical trials are not required for this. At the same time, radiation dose is generally accepted as a quantity that is correlated with

outcome; there is a fairly good understanding within the community about what different dose levels, such as 60 Gy and 80 Gy, mean in terms of tumour control and side effects. Hence, radiation dose has been used as the interface between the clinical world and the physics world. Clinicians prescribe therapeutic doses and tolerance thresholds in grays, and physicists make sure that those prescribed doses are being delivered precisely to the patient. There are some more fundamental issues with the definition of radiation dose, for example different types of radiation can have a different relative biological effectiveness (RBE) for the same radiation dose. Also, although a dose-response relationship typically exists, and physicians and physicists have a good "feel" for it, its exact shape is often unknown. Yet, in spite of these few negatives, radiation dose has been a phenomenally successful physical quantity in radiation therapy.

Bridge to fundamental discoveries and technology inventions

The most important contributions to radiation therapy have come not only from the fundamental physics discoveries such as X-rays and protons, but also from the applied physics outside the medical field, *e.g.* linear accelerators, cyclotrons and synchrotrons. A restriction to incremental technological improvements without these major breakthrough contributions from basic physics would have limited the advancement of radiation therapy substantially, to the point where it might only play a very minor and insignificant role today. The connection between basic scientific research and application in medicine is of crucial importance.

Interdisciplinary work requires generalists

Physicists are generalists. This is clearly advantageous for work in radiation therapy, which is at the interface of so many disciplines, including medicine, physics, biology, computer science and mathematics. Indeed, physicists are often very strong in mathematics, hence their success in biological and mathematical modelling, for example the modelling of treatment outcomes. Radiobiological modelling using the linear-quadratic model and the concept of biologically effective dose (BED) has been discussed in a recent review by Jack Fowler in this series [12] and will not be discussed any further in this paper. Physicists have also been very active in mathematical treatment optimisation, especially in IMRT. Here they have been particularly successful in translating radiation therapy problems into the mathematical language that can be understood by optimisation experts and that allows their dedicated tools to be applied to optimise radiation treatments. Thanks to their algorithmic minds, physicists are often very good computer programmers, which is a useful skill in an environment where computers play such an essential role. Their talent to see the "wood for the trees" helps in handling the often enormous amounts of data in radiation therapy.

What is next in dose localisation?

Although great progress has been made in the precise focusing of radiation dose to the tumour target volume,

there is still space for improvement. The future is, of course, hard to predict and there will be surprising inventions that, as in the past, may have an unexpected application and impact on radiation therapy. In this section we will discuss some of the physics challenges that remain to be solved in the field of dose localisation. These represent the areas in which we hope to see the innovations that will continue to fuel our field. This is more of a wish list than a prediction of the future of physics in radiation therapy.

Better dose localisation in space and time

The first physical challenge is related to the necessary paradigm shift away from viewing the patient as a static rigid body and towards a dynamic non-rigid representation of both the patient and the treatment machine. This requires the solution of many engineering problems, including motion-correlated imaging that reduces the motion blurring effect and effectively freezes motion, deformable image registration between different snapshots in time to track the position of each voxel in the patient as a function of time, fast-dose calculation and dose (re-)optimisation for dynamic dose accumulation, and the ability to deliver radiation in sync with patient motion (in the case of respiratory and other fast-breathing motion). Perhaps more critical than addressing fast-motion, such as breathing, is to adapt to changes that happen slowly over the course of treatment [13]. A specific problem is if, when and how to adapt to tumour shrinkage and weight loss.

In addition to these challenging engineering problems, there are also some more fundamental physics problems to be solved. These include true four-dimensional (4D) (space-time) imaging with good resolution in both space and time, as opposed to the current approach of motion-correlated CT imaging, which assumes periodicity and correlation of the motion with external surrogates. A candidate for true 4D imaging is MRI, integrated into a radiation treatment device. Several prototypes of this technology are now under development both in research and industry [14, 15]. Another physics challenge related to dynamic treatments is to develop a biophysical model of the patient with realistic characterisation of the mechanical properties of the different tissues and organs in order to simulate and extrapolate realistic motion patterns for individual patients [16].

Exploiting the physical advantage of proton (and heavier particle) therapy

Proton therapy is moving from an exotic treatment modality for very few patients to a more mainstream modality. The growth rate has been remarkably solid, over the past five decades the number of particle therapy centres has increased by a factor of 2 every 10 years (which may be considered as a Moore's law of particle therapy) [17]. The growth is based on at least one good reason, *i.e.* the preferable physical dose distribution owing to the finite range and the Bragg peak, which is the primary and undisputed advantage of proton therapy. Yet, the full potential of the physical advantage has not yet been translated into the clinic. The vast majority of proton treatments today are being delivered with the passive scattering technique, which employs

compensators and metal apertures to shape the beam. This technology (not the resulting dose distributions) resembles the technological state of the art three-dimensional conformal photon therapy from the 1980s or early 1990s before multileaf collimators and IMRT. It has been shown again and again that better dose distributions are possible with pencil beam scanning and intensity-modulated proton therapy (IMPT) (the equivalent of photon IMRT [18]). Another advantage of pencil beam scanning, although a much smaller one, is a smaller neutron contamination of the beam [19]. A technological advancement towards pencil beam scanning and IMPT to make these techniques more widely available is therefore overdue.

Proton therapy is more susceptible to various uncertainties in treatment planning and delivery, which can result in uncertainties of the proton range. The main potential advantage of proton therapy — that the beam can in principle be stopped in front of a critical structure — is therefore rarely realised in the clinic. The reduction of range uncertainties to fully exploit the physical proton advantage would have great clinical implications and is at the same time an interesting physics challenge. To that end, methods to measure the proton range in the patient include PET to visualise carbon-11 and oxygen-15 isotopes that are produced before the beam stops in the patient [20, 21]. Another method uses the change of the fat content in some organs owing to irradiation, especially in bone marrow, which can be visualised by MRI [22, 23]. The use of prompt gamma imaging has also been suggested as another means of *in vivo* range measurement [24]. For some disease sites, small dosimeters may be implanted or inserted into body cavities. All these methods have their specific limitations, and more research is needed to find a method that yields reliable and fast *in vivo* range imaging, or even dose imaging.

More efficient, more compact and cheaper treatment solutions

Radiation therapy is still a relatively cheap cancer treatment modality compared with, say, molecular targeted therapies. Yet, with all the new technology that is being used in the field, the cost increase over the years has been substantial. In particular, the case of proton therapy has been used as a negative example of how technology drives up the cost of healthcare [25]. It is therefore a worthwhile goal to use physics and technology to make the treatments simpler, faster and cheaper, without compromising their quality (*i.e.* the dose distribution).

Several developments are already under way with this goal in mind. For example, the recent development of volumetric modulated arc therapy (VMAT) has been embraced by many clinics because it promises to deliver essentially the same IMRT treatment in a much shorter time by delivering it in a dynamic rather than step-and-shoot fashion [26]. In the future we hope to see a more physical, *i.e.* scientific, approach to better understand the tradeoffs between the efficiency and the quality of a treatment [27].

Because proton therapy is several times more expensive than an advanced photon treatment [28], there has been more pressure to increase the efficiency and lower

the cost in proton therapy, even though the cost *per se* is of course not very meaningful until it has been correlated with the outcome. Nevertheless, if proton therapy were as “cheap” as photon treatments, and proton-specific uncertainties were well-controlled, there would be no question that almost all patients would have proton therapy simply for its great physical/dosimetric advantage. Therefore, several groups are developing dedicated proton treatment machines that are smaller and cheaper than current installations [29]. One approach is to develop more compact cyclotrons, synchrotrons or linear accelerators that still deliver the required clinical parameters. Interesting physical challenges arise in these developments. An even more ambitious approach is to use alternative proton acceleration mechanisms in which high-power lasers bombard thin target foils and accelerate first electrons and then protons through the electron sheath, a process known as target normal sheath acceleration [30], or, more directly, through radiation pressure acceleration [31].

Beyond dose localisation: the “new physics”

The actual role of physicists in radiation therapy goes far beyond taking the dose prescription from the clinician and making sure that this prescribed dose will be delivered to the given tumour target volume with great precision. The first and biggest additional challenge is the definition of the tumour target volume, and how to dose it.

Target definition incorporating biological imaging

Target definition is at the heart of radiation therapy problem and a critical step to achieve satisfactory tumour control. To date, target definition has been based primarily on CT. Various studies have shown that the manual contouring of the clinical target volume is highly uncertain and error-prone [32]. Target contours drawn for the same case by different physicians or by the same physician on different days show enormous differences, which puts the value of physical targeting of radiation within millimetre precision in question. A more scientific approach to target volume definition and optimally dosing the target is desperately needed. One approach is to explore incorporation of other imaging techniques in target definition to improve the accuracy [33]. Most of the attempts so far have shown a large variability of tumour delineation based on different imaging techniques [34, 35], but have provided little guidance on how to effectively reach beyond CT-based tumour volume definition. Part of the reason for this lies in the fact that methodologies for extraction of tumour volumes from other imaging modalities are not satisfactory and have led to large inherent uncertainties between different techniques [36–38]. Clearly more work needs to be done, first to better understand the pathological extent of tumours and its relation to different types of imaging; and second, to better explore ways to make imaging more quantitative than it is currently. This might involve better image analysis tools and even the development of dedicated imaging tools with a satisfactory level of imaging accuracy for the target definition problem.

The rapid expansion of functional and molecular imaging in the last decade [39, 40] and its seemingly

infinite capabilities [41] have led to speculations that biological imaging information could be used as a template for biological conformal radiation therapy — the process most often termed “dose painting” [42, 43]. While the idea is extremely appealing, many obstacles need to be overcome related to the general limitations of the imaging techniques [44, 45], but also related to the increased uncertainties when one wants to explore imaging information on a per-voxel basis to determine the extent of biological heterogeneities [46, 47]. While some of these uncertainties could be remediated by making imaging techniques more quantitative, some of the unknowns like the relation between imaging information and clinically relevant biological information will have to be established in rigorous clinical trials.

Better understanding of normal tissue response

Besides knowing what the tumour target volume is and how much radiation dose it needs, the reliable prediction of normal tissue complication probabilities (NTCP) in each organ is clearly important for both treatment planning of individual patients and assessment of the benefit of new treatment modalities. Unfortunately, this is a challenging and largely unsolved problem. Existing NTCP models are often based on the classic Emami et al [48] tables describing relationships between dose, treated volume and outcome. As these tables are now 20 years old and have several deficiencies, a comprehensive analysis of more recent data has been performed and published by the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) task group [49]. While this is clearly a step in the right direction, it is surprising that a further 20 years of research and treating patients with radiation has not produced a more solid body of data and understanding of normal tissue complications. Great care has to be used in integrating the QUANTEC results into NTCP models [50]. The difficulty in collecting solid complication data for the development of reliable NTCP models stems from multiple reasons: complications in radiation therapy are, fortunately, relatively rare; large uncertainties in the underlying historical dose and volume data (contouring of the organs) exist; and there are substantial uncertainties in the assessment of the outcome. The fact that most normal organs are non-homogeneous and that they can exhibit different types of complications (from acute reactions to the development of secondary cancers [19, 51]) further complicates matters. The advancement of alternative temporal dose fractionation schemes has shown great potential [52], but it adds another dimension (*i.e.* time) to NTCP modelling. Lastly, recent animal experiments have led to interesting insights into the “dose bath” effect [53, 54] and have challenged standard NTCP models. The addition of a very small “bath” of dose can have a much bigger effect than would be expected based on the typical assumption of a mean or maximum dose response.

Treatment response assessment and treatment adaptation

All patients are different and respond differently to radiation therapy. Yet, most of the treatment optimisation efforts in radiation therapy have been focused on a

single pre-treatment optimisation of the radiation field, largely without taking patient-individual sensitivities into account. With the increased use of imaging during therapy through anatomical IGRT the tools for treatment adaption are becoming available [55, 56]. However, this is just the beginning; molecular imaging is capable of providing even earlier feedback on treatment efficacy, thus allowing biologically adaptive therapy. So far, most of the treatment response assessment studies have been focused on correlating late imaging response with clinical outcome [57, 58], but very little is known of the early response to radiation therapy. We do not know yet when to image, how often to image and what molecular imaging methods to use. Similarly, assessment of normal tissue effects through imaging, while often displaying high correlation between imaging information and acute normal tissue toxicity, still requires more reliable imaging surrogate end points that would reliably predict long-term toxicity [59]. It is not hard to foresee the potential for rapid growth of treatment assessment and treatment adaptation, not only based on anatomical but also molecular imaging, once the initial difficulties are solved.

Implications for treatment planning: robust optimisation and multicriteria optimisation

The issue of uncertainties in target definition, treatment delivery and outcome modelling has surfaced in the previous discussion. It is important to protect patient treatments against those uncertainties. Traditionally this has been done through the addition of margins (to account for spatial uncertainties) and conservative dose prescription ("first, do no harm"), *i.e.* through manual "robustification" of the treatment plans. Computerised robust optimisation techniques have recently been developed [60–62]. These robust optimisation techniques are becoming essential in advanced intensity-modulated particle therapy [63], and especially in biologically-guided treatment planning with additional uncertainties in the underlying biological models. Also, even with the most advanced physical and biological targeting discussed above, and assuming that uncertainties can be reduced or otherwise dealt with, there is always a tradeoff to be made between target dose and normal tissue dose. Furthermore, there is typically more than one normal organ involved and tradeoffs between dosing the various normal organs have to be made as well. The standard way to find the most suitable tradeoffs for an individual patient is by trial and error. A more scientific approach uses concepts of multiobjective optimisation [64, 65], and in particular the concept of Pareto optimality [66, 67]. Interestingly, decision making with multiple objectives is a well-developed scientific field in economy and public health [68], but it has not been widely used in radiation therapy.

Does it matter in the end?

Within all the unknowns and uncertainties related to tumour control and normal tissue complications, as well as the trade-off between them, there is one steadfast lighthouse in radiation therapy, *i.e.* less dose to less volume of normal tissue is always better for the patient, if the same or more tumour dose can be delivered. This is

the guiding principle that motivates all the physical and technical developments discussed above. Now, there is an active ongoing debate about whether or not evidence has to be demonstrated in form of randomised clinical trials to prove that more focused dose delivery actually makes a significant clinical difference [69]. This issue is often raised in the context of justifying particle therapy machines against the cost explosion in healthcare [25, 70]. More solid dose-outcome models could help to answer this question. It is also interesting to explore the theoretical limits of focused dose delivery. Schulz and Kagan have published a Gedanken experiment in which they considered a hypothetical "infinatron" machine that delivers radiation dose to the tumour target volume only, and no dose whatsoever to the surrounding normal organs [70]. They argue that this device could never be better than surgery and that even such an imaginary, and probably impossible machine, would not improve the cancer cure rates substantially. However, their analysis ignores the fact that the surgical scalpel is a binary tool, whereas the "radiation scalpel" allows for a more measured approach, *e.g.* through dose painting.

Beyond radiation therapy

Traditionally, the strongest involvement of physicists in medicine has been in radiation therapy and imaging. A smaller number of physicists are already involved in multimodality therapy, especially in the modelling aspects of combined radiation and chemotherapy [71]. In the future, physicists could and should reach out to other territories that could benefit enormously from their involvement. Fast developments of life sciences in the last decades are rapidly transforming the way in which medicine is practised. Genetic screening and molecular biomarkers are having a profound impact on disease prevention, screening, diagnosis and treatment. Traditional boundaries between disciplines are being shifted and blurred by strong realisation that a complex, multifaceted approach is needed. Furthermore, the emphasis on translational research is pushing towards better merging of basic and clinical sciences. If medical physics is to remain a strong player in the future, it must not be shy of moving to these territories.

The realisation that physicists can make important contributions in many areas in medicine, especially in areas that traditionally do not normally involve physicists, has been widely recognised, but rarely acted upon. A recent initiative by the National Cancer Institute (NCI) to establish physical sciences–oncology centres was set-up to explore new and innovative approaches to better understand and control cancer by exploring a systematic convergence of the physical sciences with cancer biology. By partnering with scientists from various non-biological disciplines, NCI envisions novel approaches to help generate answers to some of the major questions and barriers in cancer research. NCI's initial goal was to join these often disparate areas of science by building a collaborative network composed of physical sciences–oncology centres. Working in cross-disciplinary teams, those centres will explore the physical laws and principles that shape and govern the emergence and behaviour of cancer at all scales in an effort to open up new areas and support the development of clinical

advances. While this is only the first initiative, it is certainly not the last one.

Part 2: physics role-challenges and future

“As for the future, your task is not to foresee, but to enable it” (Antoine Saint-Exupéry).

The mission of medical physics profession is clear — to answer the clinical problems that arise through patient care by understanding and developing medical technology, providing physics expertise and employing critical scientific thinking. Most medical physicists can relate in one or another way to measurement, quantification, analysis or interpretation of technical and patient data. Physicists are often (but arguably not often enough) active partners of radiation oncologists and help them to decide how much dose to give, where and when. Specifically, clinicians and physicists work together on the design of treatment plans for individual patients, as well as on the design of clinical trials to answer scientific questions. With such function, medical physicists are an essential and critical link in the patient management chain, gaining more prominent importance as the technical complexity of patient care continues to increase.

What is the role of physics?

This mission is accomplished by medical physicists playing a spectrum of different roles with two distinctive extremes: the clinical role, with the primary goal of securing safe clinical operation of medical procedures; and the research/academic role, with the primary goal of academic development of the medical physics field (Figure 2). The spectrum of medical physics roles can be further divided into subcategories, each employing a different proportion of medical physicists.

The majority of medical physicists, in the order of 80%, are primarily focused on clinical implementation, with little or zero research/academic component. This group of medical physicists, typically working in hospitals, of whom the majority are employed in clinical radiation oncology departments, provides a sound and successful foundation for safe, reliable and accurate use of advanced technology in clinical setting. While typically not generating new knowledge *per se*, this group needs to be informed of new advances in the field and new technological developments. The professional foundation for this group of medical physicists is well established, typically following the same rules as the medical profession by requiring stringent professional board certification and continuing professional development.

A smaller subset of medical physicists, in the order of 10%, is still carrying a primarily clinical role, but has started to bridge towards research. However, most of their research, is limited to solving day-to-day problems, resulting in predominantly clinical technology improvements. While research is not the major emphasis or goal, the on-the-job problems might also require innovative approaches and novel solutions, but with often limited time dedicated to research, it cannot really lead to major advances in the field. The professional development of

Figure 2. Spectrum of medical physics roles. Each of the four primary roles: cutting-edge research, translational research, technology improvement and clinical implementation, are equally important, even although they are not, and do not need to be, equally represented.

this group follows the same path as the “clinical practice” group.

On the other side of the spectrum there is a small minority of medical physicists, probably less than 1%, with a main research/academic focus, and primary role to perform cutting-edge research. The time horizon of this research is typically 10–20 years or more. In contrast to the clinical practice group, the professional foundation for this group of physicists is not well-established. While there are several outstanding institutions worldwide doing excellent medical physics research, the trends show increasing difficulties for sustainable performance of this group, in a large part owing to the absence of a well-organised academic path.

With the predominantly research role, a much larger fraction of medical physicists, in the order of 5%, could be characterised as performing translational research, that is primarily performing high-quality research in newly identified and expanding areas, often linked to direct clinical application. The time horizon of the research for this group is in the order of 5 years. Most of the medical physicists in this group are strongly confined to a specific medical physics subfield (e.g. radiation oncology), often preventing them from easily bridging across to other medical physics subfields as well as towards other professions. Most of the medical physicists in this category still enter the field more or less randomly and without a dedicated, well-organised academic path and guided career development.

Of course one should be aware that such division is rather simplistic, and while it might be possible to clearly identify some medical physicists with a particular category, the boundaries are rather blurred and people might move from one to another category (e.g. between cutting-edge research and translational research, or clinical practice and technology improvement). It is equally important to emphasise that none of the categories is better or more important — medical physics needs all and everyone. Without solid clinical practice there would be neither room nor need for research, and not just in medical physics itself, but also clinical and other basic scientific research enabled by medical physics. For example, radiation therapy dose accuracy

and precision of delivery is now, thanks to the extremely high standards of clinical practice, of such a consistently high order that it is taken for granted. Yet, without that, far less credence could be placed on the results of clinical trials and many of the new clinical developments in radiation oncology would founder. Similarly, without strong research, development of novel technologies would not be possible. Furthermore, to have an efficient and solid medical physics profession, each of the areas has to be adequately represented, strong and healthy.

We can see the connection between all four areas as a chain — the “thickness” of each link representing the “healthiness” of each area, measured in the adequate number of people working in the particular area and the “length” of each link representing the time it takes for the idea to move to the next area (Figure 3). Clearly, not having an adequate number of people working in each area leads to a weakening and lengthening of that particular link, as well as of the whole chain. It is crucial that when we discuss the future of medical physics we make sure that each of these links is covered and taken care of adequately and sufficiently.

What are the challenges?

While medical physics is currently going strong and one could argue that there is nothing to worry about, further thought reveals several challenges, which, if not properly addressed, may lead to a diminishing role, followed by destruction and fall of the whole medical physics field. We are beginning to see negative symptoms on the research side. It is clearly becoming harder to find good research-orientated medical physicists at the post-doctoral level. Some of the reasons and possible solutions are discussed below. The research grant funding situation has become very hard owing to the worldwide economic troubles, even although some of the recent signs are more positive. The impression shared by many research medical physicists is that the quality of the medical physics research presented at many conferences and in scientific papers is declining,

Figure 3. Optimal medical physics chain. Each of the links should be equally strong for optimal development of the medical physics field. Weakening of any of the links will result in prolonged time from the discovery to clinical implementation, and a break of any of the links would lead to the break and fall of the whole medical physics field. Time scale is approximate and indicates approximate time horizon of each of the component of the medical physics spectrum.

even although it is hard to provide hard data for it. The major scientific journals, *Physics in Medicine and Biology* and *Medical Physics*, are still performing strongly, but it may be an indicator that the most recent impact factor (ISI) for *Medical Physics* from 2009 has, for the very first time, dropped substantially, by 30%.

One of the biggest challenges is the mismatch between the current educational structure of medical physicists and typical role that medical physicists are playing. According to a survey of the American Association of Physicists in Medicine (AAPM), the majority of medical physicists are currently at the PhD level. While a PhD is necessary to perform research, it is clear from the previous discussion that the majority of medical physicists are not involved in research, at least not the research at the level that would result in scientific publications or research grants. This situation means that we currently experience an overflow of overqualified and academically overtrained medical physicists, with poor prospects for the future, which will naturally lead to the equilibrium, especially in radiation oncology, requiring fewer PhDs.

The technological orientation of clinical medical physics is reflected in the fact that more and more services, traditionally performed by medical physicists have been transmitted either to other professions (e.g. dosimetrists, technologists), or even outsourced to the companies. While medical physicists sometimes do not want to admit that their level of education and expertise might be too high, it is increasingly realised by the hospital management when less skilled (and less expensive) professionals are put in place instead of medical physicists. It is expected that this trend will continue.

In addition, many PhD-level medical physicists enter the clinical world through the “back door” without proper professional practical training. As such, medical physics stands out among other medical professions. This situation has been realised in the United States by the main medical profession certification body, the American College of Radiology (ABR), pressuring the medical physics community to provide adequate clinical training. Part of the response to the so-called “2012/14 ABR requirements” has been through establishment of the professional Doctorate of Medical Physics (DMP) degree, which would provide masters-level academic training followed by organised practical training. One might debate whether a DMP is actually the correct title, or whether Doctorate of Medical Technology might be more appropriate, since most of the training is aimed at mastering technology rather than physics.

While the clinical arm of medical physics seems to be getting appropriate attention and training, the research/academic arm does not. The medical physics profession as a whole is lacking organised academic training. Most of the medical physicists hold BSc degrees in physics, but their MSc and PhD training is often in a different physics specialty, traditionally nuclear or particle physics, or engineering. While this might have been acceptable in the past when the professional training requirements were less stringent and when medical physics was smaller and one would acquire necessary practical training “on-the-job”, it would be hard to argue that this is still acceptable. Strong, rigorous and focused

academic medical physics training is absolutely essential. However, only taking care of graduate education is not enough, medical physics should also precipitate to the undergraduate physics level. At present, finding physics departments that have medical physics as part of their undergraduate curriculum is almost impossible. Clearly the situation has to change.

One can summarise this situation by referring back to Figure 3. While the technology improvement and clinical implementation of the medical physics chain appear healthy (and perhaps even overpopulated), the cutting edge research and translational research areas, at least in radiation therapy, are not (Figure 4).

Additional challenges

Even though medical physics is well-accepted in the medical field, it is still surprising how much it has to fight for acceptance in the physics field and continue to prove that it is “real” physics. Perhaps this is due to the fact that most of the “real” physicists predominantly see the clinical part of medical physics, where the focus is not research, but rather clinical practice. The problem may also lie in the fact that medical physics has never cared much about promoting itself back at the roots, *i.e.* in physics departments, as it was busy searching for acceptance in the medical community. As medical physics is in essence interdisciplinary, lying between physics and medicine, it is not surprising that it has found its home in medical departments. However, what is surprising is that it has found its home much more frequently in medical departments than in physics departments. We do not consider this to be a good long-term survival strategy. We believe that medical physics has the potential to become one of the most exciting, challenging and rewarding clinical and academic physics disciplines, and that it should be promoted as such.

Interestingly, even though medical physics is well-accepted in the medical field, it is not necessarily equally well respected, certainly not universally. For example, while medical physics is generally well respected in the UK and the United States, it is much less so in Germany. Why? The reason is partially owing to the differences in

social hierarchy between different professions and partially in how well medical physics is organised and promoted in different countries. While influencing the social structure and relationships is a hard and slow process, organisation of the medical physics profession and its promotion should be at the top of the to-do list of any national medical physics society.

Challenges beyond radiation therapy

While the discussion above applies in one way or another to the whole field of medical physics, it is geared toward physics in radiation therapy, like this whole article. There are also specific challenges that come with the “new physics” outside the traditional domain in radiation therapy and radiology. The first challenge is to learn how to talk to other disciplines. While medical physicists are traditionally used to having a strong interaction with physicians, particularly radiation oncologists and radiologists, they will have to learn to communicate effectively with other basic and clinical disciplines. This might seem an impossible task, without diluting the knowledge and expertise that medical physicists have, but one has to realise that this merge is happening first at the level of cutting-edge research for a small fraction of the most “adventurous” scientists. Similarly, as in medical physics, other disciplines face the same spectrum of roles in their professions; this is outlined in Figure 2. Driven by their scientific approach and curiosity cutting-edge research medical physicists connect more easily with cutting-edge research scientists in other disciplines. They all share the same approach and are therefore by their nature on the same wavelength. Finding a common language with the same-thinking researchers from other disciplines should be easier than it appears at first, and this is where the bridges should be built. There is one obstacle to this, that is, people in different fields often do not communicate at a simple enough level for these bridges to be built. There are too few researchers who dedicate time to developing the necessary skills to communicate fundamental concepts in simple ways, and this may be partly because people feel that this threatens their integrity. Nevertheless, once initial smaller bridges are formed, they will naturally be enforced and consolidated through extensive common research. If the research proves fruitful, the clinical practice will naturally follow. Of course, in order to facilitate such endeavours beyond traditional medical physics boundaries, medical physicists should not wait to be called, but should take an active role in approaching other professions, actively searching for collaborations and actively trying to find synergies.

Medicine in general is influenced not only by physics but also by biology and other basic sciences. One could argue that this might lead to a decrease in the relative importance of physics, although absolute contribution stays at the same level. Regardless, medical physicists need to embrace other disciplines as well as new territories outside radiation oncology and radiology. This might not be an easy task, without diluting the primary (*i.e.* physics) training and knowledge. However, while intensifying the curriculum in non-standard subjects might not be appropriate for the majority of medical

Figure 4. Suboptimal medical physics chain. Currently we are experiencing an increased emphasis on consolidating the clinical part of the medical physics spectrum, leaving the research part behind. This leads to the prolongation of the time between invention and clinical implementation, particularly severe as the relative time scale is not linear.

physicists, those who are “cutting-edge” should definitely invest extra time and effort into interdisciplinary training beyond the typical medical physics training curricula.

Vitalising research in medical physics: two suggested solutions

Given the current focus on the professional, non-scientific side of medical physics and the fact that radiation oncology has relied so much on the application of the scientific method as well as on the groundbreaking innovations coming from physics and medical physics, there is a risk that radiation oncology will “dry out”, and medical physics with it. Some have argued that radiation therapy physicists have already become glorified technicians [72]. Those few clinical physicists with protected research time of, say, 1 day per week cannot be expected to invent the next CT or IMRT. It takes more quality time to take a step back from the busy clinical environment, look at the bigger picture, ponder ideas and test them out. It also needs the right creative environment, a “playground” to explore new ideas and cross-fertilise within a group. A good first step could be to allow physicists to take sabbaticals of 6-12 months to dig deeper on a problem or idea that they had, perhaps during their clinical service. However, this is very difficult if not completely impractical in small departments. We believe that a long-term solution to the problem of the lack of research focus has to include the creation of a research and academic career path in medical physics, in parallel to the existing professional track. A fundamental requirement for that is to create more research positions and establish more academic programmes in medical physics. How can this be accomplished?

Create more research positions

The first option is to create research positions (with >80% protected research time) in the hospital environment. To create a new research physics position will certainly face some resistance from the department chairs and hospital administration. One of the first questions will be why create a research position for a physicist and not, for example, a biologist or clinical scientist. Based on what we have said above, we believe that convincing arguments can be made in support of a position for a physicist. The bigger question is perhaps where the funding should come from. Here it should be made clear that only the start-up money would be needed since the research physicist, if successful, would be self-supporting. The research physicist would eventually be making money for the department by stimulating research involvement of other members of the department, which would lead to additional funding. The start-up funding could come from the physics contributions to the profit of the department, which is often substantial. All of this is not an easy process, especially in the current funding climate, but there are several examples where it has been done successfully.

Another option within the hospital environment is to convert a vacant clinical position to a research position.

Naturally, this can only be done in bigger departments with more than five physicists. Even then, this option will face resistance from the other clinical physicists who will have to pick up the extra work. Nevertheless, there are examples where this option has worked with great success and those examples can be used as role models. The benefit for the group include cross-fertilisation between the clinical and research physicists, the creation of a more interesting work environment and the fact that the research may in fact help to make the clinical processes more efficient and save time.

More research physicists are also needed at the junior faculty and post-doctoral level. In the United States the 2014 ABR requirements that prevent post-doctoral staff from moving on to the clinical path have made it difficult to fill post-doctoral positions. Many PhD physicists interested in medical physics prefer the well-established path of doing a physics residency in a hospital to a post-doctoral position with uncertain career prospects. Until the academic career path in medical physics has been fully-established, an intermediate solution to recruiting research physicists at the post-doctoral level might be to create a hybrid residency-post-doctoral position. The price for that is a prolonged training period, but the candidates will benefit from the extra research exposure in their clinical career, and it will keep the option open for them to pursue a research career later.

Another option for creating more research positions is to join forces with physics departments. While this might seem like the most straightforward solution, it is obviously not a trivial one; otherwise we would have witnessed much more synergy between medical physics and physics departments so far. To overcome the difficulties, we have to understand what the major barriers are. Probably the most important obstacle is that neither physics departments nor clinical departments see enough value to overcome the initial investment threshold to collaborate effectively. In addition, medical physics is by definition an applied science, while the majority of physics departments find themselves more on a basic science track. While medical physics is undoubtedly applied science, the number of Nobel Prizes given to the medical physics type of research is proof in itself that medical physics research can promote and develop basic research as well. A big part of the solution lies on the shoulders of medical physicists who should promote medical physics as an academic career within physics departments. Promotion of medical physics should result in the creation of new faculty positions in physics departments that should in turn attract good students and post-doctorates who see medical physics as the ultimate career choice. This would start a positive spiral of influx and self-sustained level of high-quality researchers in the field.

While creating positions within physics departments is an attractive idea, one should be aware that medical physics researchers definitely need access to clinics. This can be created by securing a strong strategic link between medical physics researchers within physics departments and their clinical collaborators. Alternatively, it might be more practical to create hybrid positions between physics and clinical departments. Such an arrangement would be very attractive for both sides. The physics departments could see such researchers as the

portal to the real-life problems in the clinics, facilitating access to clinical data and medical research funding. The clinical departments could see such researchers as full-time investigators, with time, desire and mission to initiate and promote the best research that will ultimately help clinical practice as well.

Create more academic programmes

Creating more research positions could be seen as a short-term strategy to improve the quality of medical physics research. However, long-term improvement can only be created by starting at the source *i.e.* from academic programmes. While there might not be enough room for many academic medical physics departments because of servicing to mostly graduate level scientists, the need is large enough to warrant many more academic programmes than currently exist. In general three types of academic programmes could be created: independent medical physics departments, medical physics programmes within clinical departments and medical physics programmes within physics departments.

Creation of independent medical physics programmes is not easy. There should be a critical mass of medical physicists that can support all the academic activities, *i.e.* teaching, mentoring and research, in one place. In addition, these physicists should be well-integrated into the clinical practice so that the connection to the clinical problems would be at the heart of research activities. In the current situation, this would only be possible if departments were created by connecting the physicists already employed at clinical departments, who would have joint appointments between the two departments (academic medical physics and the clinical department). This solution is of course limited to large academic clinics and large cities with multiple academic centres that can provide such a critical mass of academic researchers. As the creation of any new departments carries significant consequence, the case should be made carefully and only where the environment is ready to support such an endeavour.

An alternative solution would be to create medical physics academic programmes within the existing clinical or physics departments. In clinical departments this would require a large number of research orientated physicists, without excessive clinical duties, who could devote a substantial amount of time for academic duties. It would also require convincing the medical school leadership that such a programme could bring an added value to the school as a whole. Medical physicists have proved to be some of the most proliferating researchers in medical schools, generating exceptional levels of extramural funding revenue, but again, this depends strongly on the local environment. If there is a large group of well-funded, research-minded medical physicists within a single clinical department, or multiple departments, or even multiple clinics geographically close, such a solution is definitely an option and should be encouraged. The biggest challenge for such a programme would be to establish a strong relationship with an academic physics department, which should provide adequate access to university resources.

Establishing medical physics academic programmes within physics departments would require a large

number of existing physics faculty members who have at least some interest in medical physics. This option would only be feasible in large physics departments, or small physics departments that decide to make medical physics one of their priorities. Interestingly, drawing from the experiences of programmes that took this path, it often occurs that students with a high interest in physics in medical research, linked with relatively good employment opportunities, make medical physics programmes grow well beyond what they were initially intended for, easily exceeding 20% of the whole physics department. It really boils down to the question of how to convince the leadership that such a programme will not damage the existing programme, but rather enhance it (*i.e.* bring in more students and research funding). An alternative to establishing academic programmes within physics departments is to establish medical physics programmes within engineering departments (*e.g.* nuclear engineering, biomedical engineering). However, as current experiences indicate, this might not necessarily be a good long-term solution, probably owing to the inherent differences between physicists and engineers. Some form of symbiosis with engineering departments is possible, and likely to be very productive, but it is important to acknowledge primary differences between the two disciplines. The biggest challenge for an independent medical physics programme within physics departments would be to establish a strong relationship with clinical departments, which should provide adequate access to clinical resources, particularly equipment and clinical data.

When considering new academic programmes one should not skip a very important question — how should medical physics programmes of the future be designed? It is clear that current programmes are not optimal. They are a mix of programmes that have trained students for both professional and research careers. In the United States, this “redundancy” was first realised by the professional part of medical physics, creating professional medical physics programmes, which would lead to DMP professional degrees. This training eliminates, to a large degree, research and any courses that do not directly lead to clinically useful knowledge. Creation of these programmes should actually be the last call for academic programmes that want to train students for the research part of the spectrum. Research medical physics curricula should be modernised by adding components of training that modern research requires, including collaborative, interdisciplinary and translational research components. One could of course argue that no programme would be good enough for the small fraction of students that will be in the “cutting edge research” category (Figure 2). What research academic programmes really need to serve are the students who fall into the “translational research” category. However, one could equally argue that even the top “cutting edge research” students who will move the field forward and eventually secure the long-term survival of medical physics need to learn how to do high-quality research, how to interact with others and how conform to the high-standards of responsible scientific research.

The bottom line

The strong standing of radiation therapy today is based substantially on physics research from the past.

The scientific method has played an important role in this evolution over the past century. New challenges and opportunities are waiting for research orientated physicists in the traditional domain of radiation therapy, as well as outside of it. However, the current focus on the professional side of medical physics away from research makes it more difficult to address those future challenges. Radiation therapy as a field is biting the hand that feeds it. Proliferation of medical physics training programmes focused on professional development further dilutes the high-end research strength of the field. We are missing strong, rigorous and focused academic medical physics training programmes. We are missing academic research environments that will secure a sustained long-term influx of new research ideas and overall development of the field. This imbalance is severely jeopardising the long-term future of medical physics. Every effort is needed to change this to ensure the future remains as bright as the past, and medical physics remains one of the most exciting professions.

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