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Roadmap: proton therapy physics and biology

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Abstract

The treatment of cancer with proton radiation therapy was first suggested in 1946 followed by the first treatments in the 1950s. As of 2020, almost 200 000 patients have been treated with proton beams worldwide and the number of operating proton therapy (PT) facilities will soon reach one hundred. PT has long moved from research institutions into hospital-based facilities that are increasingly being utilized with workflows similar to conventional radiation therapy. While PT has become mainstream and has established itself as a treatment option for many cancers, it is still an area of active research for various reasons: the advanced dose shaping capabilities of PT cause susceptibility to uncertainties, the high degrees of freedom in dose delivery offer room for further improvements, the limited experience and understanding of optimizing pencil beam scanning, and the biological effect difference compared to photon radiation. In addition to these challenges and opportunities currently being investigated, there is an economic aspect because PT treatments are, on average, still more expensive compared to conventional photon based treatment options. This roadmap highlights the current state and future direction in PT categorized into four different themes, 'improving efficiency', 'improving planning and delivery', 'improving imaging', and 'improving patient selection'.

Contents

1. Introduction to the proton therapy (PT) roadmap

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The dosimetric advantages of proton radiation therapy compared to 'conventional' photon radiation therapy were first outlined by Wilson in 1946 (Wilson 1946). He presented the idea of utilizing the finite range of proton beams for treating targets deep within healthy tissue, and was thus the first to describe the potential of proton beams for medical use. Wilson's suggestion to use protons was based on the well-known physics of protons as they slow down while penetrating tissue, causing the Bragg peak and completely stopping in the patient.

While the advantage of protons was seen from a physics (dosimetric) perspective, any new radiation treatment technology has to find acceptance amongst clinicians by demonstrating that the improved dose distribution leads to a more favorable treatment outcome (Suit *et al* 1975). When PT was first introduced it was of interest mainly because it showed dose conformity far superior to any type of conventional photon radiation therapy at the time (Suit and Goitein 1974, Suit *et al* 1977). The difference in target dose conformity between protons and photons, at least at high doses, has however largely disappeared since the early days of PT (at least for regularly shaped targets), mainly due to the development of intensity-modulated photon therapy and its extension to rotational therapies. Today, it is quite feasible to reach high-dose conformity to the target with photons that is comparable to the one achievable with protons, albeit at the expense of using a larger number of beams. However, the integral dose (the total energy deposited in the patient) is always lower with proton beams (by a factor of at least 2–3 (Lomax *et al* 1999)), i.e. proton treatments avoid the 'dose bath' to healthy tissue that patients are exposed to with photon techniques. Indeed, there is a limit to further improving and shaping photon generated dose distributions because the total energy deposited in the patient, and thus to critical structures, cannot be reduced but only distributed differently. Proton radiation therapy, on the other hand, can still achieve further improvements through the use of scanning-beam technology and intensity-modulated PT (IMPT).

PT is already an established treatment option for many tumor types and sites. For instance, it is well recognized that protons are extremely valuable to treat tumors close to critical structures, e.g. for head-and-neck treatments (Chan and Liebsch 2008). In the pediatric patient population, the impact of the decreased total absorbed energy in the patient with protons seems most significant. The overall quality-of-life and reduction of secondary effects is particularly important and the reduction in overall normal tissue dose has proven to be relevant for short and long term toxicities (Indelicato *et al* 2019, Xiang *et al* 2020). One prime example is the treatment of medulloblastoma, where treatment with photon radiation therapy invariably causes significant dose to the heart, lung and abdominal tissues, as well as organs at risk (OAR) in the cranium, something that can largely be avoided using protons (Kamran *et al* 2018). The reduced integral dose with protons is also beneficial when radiation is combined concurrently with chemotherapy (Baumann *et al* 2019). Nevertheless, there are still many circumstances and treatment sites where the advantage of protons appears to be marginal at best (Lee *et al* 1994, Liao *et al* 2018). Thus, it is debatable whether the dosimetric advantages of PT are clinically significant for all treatment sites, warranting the various randomized clinical trials comparing protons and photons that are currently being conducted for sites such as breast, prostate, lung, and many others.

There is thus much that still needs to be done to fully exploit the physical advantages of protons. As such, this roadmap focusses on physics and biology aspects that are currently, or should be in the future, the subject of major research and development projects. Other aspects that are already clinical reality or are well on their way to being clinical standards (e.g. Monte Carlo (MC) based dosimetry for planning and quality assurance (QA)) will not be addressed in detail. Furthermore, as most centers will be treating with beam scanning in the near future, passively scattered PT is not discussed, even if many of the innovations highlighted in this roadmap are independent of the delivery method.

The targeted audience for this roadmap are the readers of Physics in Medicine and Biology. Accordingly, except when relevant in the context, we are not discussing specific clinical applications of PT. Similarly, although the health economics and resulting societal impacts of treatment with PT is a highly interesting and controversial field, we have not included articles specifically related to this or other societal impacts. With that said of course, many of the topics discussed here, such as efficiency gains and identifying those patients most likely to benefit from reduced side effects or improved tumor control with PT, would be expected to reduce overall health care costs.This roadmap instead highlights the current state and future direction of PT from the physics and biology aspects, in which we have categorized the articles into four different themes, 'improving efficiency', 'improving planning and delivery', 'improving imaging', and 'improving patient selection'.

Improving efficiency

PT is a currently expensive treatment modality. Nevertheless, the cost of a proton treatment is expected to decrease with increasing number of facilities, and many developments in accelerator technology are focusing on lowering initial investments when acquiring a PT facility by providing single room treatment facilities or even facilities without a gantry. Extensive work is being done also on improving beam delivery efficiency to reduce operating costs. These developments should of course not compromise the achievable dose conformity.

As such we have four roadmap contributions dealing with treatment efficiency; 'Cost reduction by optimizing accelerator technology', 'Technology for delivery efficiency', 'Delivery technology', and 'Efficient treatment room utilization'. While not directly evident, roadmap contributions in other sections such as those concerning the biological effectiveness of proton beams as well as biomarkers may also contribute to improved cost effectiveness in the future. For instance, identifying patients most likely to benefit from reduced side effects or improved tumor control (based on tumor genomics) with PT would be expected to reduce health care costs for society overall.

Improving planning and delivery

In comparison to IMRT or VMAT, there are typically many more degrees of freedom for modulation in PT, due to the three-dimensional distribution and application of individually weighted Bragg peaks. These additional possibilities are only just beginning to be explored, and much can still be done in the treatment planning process to best exploit these possibilities to improve treatment precision and accuracy. On the other hand, tissue deformations can significantly affect proton ranges in the patient so that PT is generally more affected by intra and inter-fractional anatomy changes. Reducing uncertainties is thus a key research theme in PT physics, as is the proper quantification, monitoring and reporting of uncertainties. Adaptive therapy has a higher potential for clinical impact in PT compared to conventional radiation therapy. Uncertainties also exist in the biological effect of proton beams. As uncertainties can never be eliminated entirely, optimization techniques are being developed to reduce their clinical impact.

As these topics are currently researched heavily, there are seven roadmap contributions in this category: 'Uncertainly precise—uncertainties in PT and how to tackle them', 'Treatment planning', 'Development of robust planning', 'Adaptive therapy to account for daily anatomy and range variations', '*In vivo* range verification', '4D planning and delivery', and 'Considering the relative biological effectiveness (RBE) of protons'.

Improving imaging

Modalities for pre-treatment diagnostic imaging are impacting all radiation therapy modalities. Even though originating in PT in the 1960s and 70s, in-room imaging is currently more advanced in conventional radiation therapy. It is expected to make a bigger impact in PT because of dose deposition uncertainties warranting treatment monitoring more closely but also because of dose-shaping capabilities with PT that make small corrections both necessary as well as achievable. Furthermore, there are various efforts to improve tissue characterization for dose calculation in adaptive workflows.

There are two roadmap contributions about 'Advances in imaging for proton treatment planning' and 'Image guidance (IG)'.

Improving patient selection

There is an ongoing discussion about the necessity for randomized clinical trials to show a significant advantage in outcome when using protons in favor of photons. It is likely that for specific sites, PT might be advantageous only for a subset of patients and model based trials to stratify patients into randomization have been suggested and are already being implemented at some centers. This raises the question about the applicability of dose-response models developed from photon treatment outcomes. Additionally, in the era of precision medicine, patient selection based on biomarkers is playing an ever-increasing role. We are just starting to scratch the surface of identifying sub-populations for (proton) therapy based on biological/genetic fingerprints. This has to be understood also in the context of (systemic) treatments prescribed in addition to radiation therapy. Indeed, maybe the most important areas for progress in PT may lie in improving our understanding of differences in biological responses to proton versus photon treatments. In areas such as predicting biological response based on genomic features, very little is known. Many of these developments are not necessarily specific to PT. As such roadmap contributions about 'Selection of patients for PT', 'Outcome modeling for PT', 'Biomarkers in PT', and 'Systemic effects of PT' have also been included.

Summary

Research and development in PT is a topic of increasing interest in radiation therapy physics, medicine and biology, with the number of research articles about PT greatly exceeding the number of photon therapy related

manuscripts when considering the tiny number of patients under treatment. How this will develop in the future is the subject of this roadmap, which collects the opinion of leaders in the field and their vision on how this treatment modality will advance in the near future. As such, there are many personal opinions contained in this article, and opinions that not all readers will necessarily agree with. But that of course 'is the nature of the beast' when different experts are asked to take a look into the future. In addition, in order to catch a true 'snap shot' of current thinking, other than providing broad titles to the different contributors, no detailed guidelines on content were provided, to not restrict their creative thinking and writing. Similarly, the contributors were not provided access to other contributions before submitting to the roadmap collection. As such, there are inevitable overlaps between some contributions. If a topic is mentioned more than once, and completely independently by different authors, does this not add an important, and not to be ignored, emphasis to that point?

Part 1: Improving efficiency

2. Cost reduction by optimizing accelerator technology

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Introduction

For routine clinical application of PT, the cyclotron, synchrotron and synchrocyclotron will be the most commonly used accelerators in the near future. Although some developments are still aiming at a technical improvement, in general, these accelerators are considered to have reached a mature state, and that they have been developed sufficiently for their application in PT. Therefore, in the coming years most improvements of these machines will be focussed on a cost reduction of the manufacturing and service. A reduction in size of the accelerator is regarded as a key issue in price reduction by the commercial suppliers of PT accelerators. In parallel to these industrial developments, one is also working on a PT application of recent accelerator developments in various research institutes and laboratories. After discussing the developments in synchrotrons and cyclotrons, these will be summarized shortly.

Synchrotron

Since the first phases of PT, synchrotrons have been used and have been further developed specifically for this application. Proton-synchrotron accelerator systems are composed of a proton source and a linac (linear accelerator), which injects the protons into the synchrotron ring for acceleration. The synchrotron ring consists of several bending magnets and magnetic lenses. In the RF cavity, which is also mounted in the ring, an oscillating electric field is generated to accelerate the protons. The ring has a typical diameter of 6–8 m and the injector has a length of 6–10 m. The maximum number of protons that can be injected into the ring is limited (in the order of 10^9–10^{11}) but this number increases with the injection energy. A higher filling of the ring is still an important research topic, since for the application of one field at the patient, one typically needs 1–3 fillings and acceleration sequences (Hiramoto *et al* 2007). Therefore, a higher filling of the ring would reduce the treatment time considerably. The beam extraction process in a synchrotron for PT, has been improved by the RF-knock-out technique (Hiramoto *et al* 2007). With this technique the beam shape and intensity remain more
constant during the extraction of the beam, which is of great advantage in controlling the dose application procedure.

The most important cost drivers that are specific for each synchrotron type, are the ring diameter (i.e. the amount of magnets and their strength), the proton source, the injection system (injection Energy) and the RF system. Cost drivers related to the synchrotron are the footprint, systems to match the beam shape to the gantry angle and the ring filling and ramping time, which determine the averge dose rate at the patient (i.e. treatment time).

Smaller (and thus cheaper) synchrotrons, with diameters down to 5 m have been developed in the last decade (Wang *et al* 2011, Umezawa *et al* 2015). Also, the footprint of several synchrotron facilities has been reduced by optimizing the layout of the ring, proton source and injector and by combining the proton source and first acceleration steps (Vretenar *et al* 2014). A further cost reduction has been achieved by reducing the number of synchrotron elements and the differences between the individual magnets in the system.

A very significant improvement has been achieved in one of the synchrotrons for carbon therapy, by enabling a reduction of the beam energy during the beam-extraction phase (Iwata *et al* 2010). This is of optimal benefit for the necessary energy variations to cover the target in depth. This development, which is being implemented in some proton synchrotrons as well, can reduce treatment time by 30% in synchrotron facilities (Iwata *et al* 2010). Another development shortening the treatment time, is expected from an increase of the ramping speed of the synchrotron magnets (Trbojevic *et al* 2011). Although similar important improvements in facility operation are expected soon, no substantial facility size reductions are expected in the near future in facilities driven by a synchrotron. However, developments are continuing and these will optimize the synchrotron operation and yield a gradual cost reduction.

Cyclotron and synchrocyclotron

Since the last 25 years also cyclotrons are commercially available for PT. These are single magnet machines, with a typical diameter of 5 m and a weight of 200 tons, which accelerate protons to a fixed energy. With a degrader followed by an energy selection system, all necessary lower energies can be obtained in a fast procedure. During the last decades important technical developments have been implemented into cyclotrons for PT, so that several types of cyclotrons can be achieved nowadays. The differences in cyclotron costs are mainly related to differences in its size or mass (i.e. the amount of iron), superconducting (SC) coils or not, the RF system and the hardware and control of beam-quality determining components. Other cost drivers related to the cyclotron are the energy selection system, shielding and activation.

To reduce the size of a cyclotron, a stronger magnetic field is needed. This is only possible by using a superconducting magnet. The first SC cyclotron in PT (Schillo *et al* 2001) has a diameter of 3.5 m and a weight of 100

tons. Further developments have enabled even stronger magnetic fields. Very small so called 'synchrocyclotrons' of only 30–50 tons and a diameter 1–2 m, have been produced and taken into clinical operation in the last decade (IBA Website 2019, MEVION Website 2019). As expected, this has led to a significant reduction in the price of a cyclotron. For one type of these cyclotrons, its mounting on a rotating gantry (MEVION Website 2019) has decreased the facility footprint significantly.

However, contrary to the traditional 'isochronous' cyclotrons (either with normal or with SC magnets), providing a continuous proton beam, the very small synchrocyclotrons can only operate in a mode with a pulsed proton beam. Their maximum pulse rate of 1 kHz imposes limitations on beam intensity (i.e. dose rate), so that one cannot have very short treatment times. Although the average beam intensity is limited, during the pulse the beam intensity can be quite high. At several sites this has be used for experiments in which small volumes have been irradiated with the very high dose rate in a pulse. Also, the expected very beneficial dose delivery techniques used to provide continuous pencil beam scanning, are not possible with the pulsed beams from these synchrocyclotrons. To prevent these limitations and to reduce the costs related to the facility footprint, several companies now offer a single-room facility with a compact arrangement of a gantry with an isochronous cyclotron, providing a continuous, well controlled beam intensity.

In the field of SC cyclotrons, studies have also been started to design a synchrocyclotron with a magnet that has no iron yoke (Radovinsky *et al* 2014). This would reduce the mass of a cyclotron by a factor 10. However, since these ideas are still at an early design stage, no estimates on price and availability can be made yet.

Other accelerator types

Novel proton acceleration concepts based on e.g. lasers are being investigated. In laser based accelerators (Zeil *et al* 2013), major topics one is working on are: a very high beam power, a reasonable short repetition rate of the laser pulses, a sufficiently high proton energy and the energy spectrum of the protons created by the laser.

Other developments are focussing on a beam optics concept of fixed magnetic fields and alternating magnetic gradients. Both in accelerators and in some gantry designs, one is applying a beam optics based on strong magnetic fields of alternating polarities and gradients (Trbojevic *et al* 2007 and Sheehy 2016). This has the advantage of large energy acceptance. Much effort is put in the construction of the tight packing of the very strong magnets of opposing polarities in a gantry design and a reduction of the power of such a fixed field accelerator. This accelerator is based on such a beam optics of a ring of magnets with fixed fields having alternating strong magnetic gradiens. It is a synchroton like accelerator, but with fixed magnetic fields, similar as in a cyclotron.

The first linac for PT has been developed from ideas used in high-energy physics and is almost ready for installation at a clinical site (Degiovanni and Amaldi 2014). An important advantage of a linac would be the possibility for rapid energy changes for range modulation. In a linac one can simply switch off or change the power in one or more acceleration cavities.

Although these developments are very important, for many of them still many steps have to be made before they are ready for implementation into a clinical facility. In addition to that, it is not clear yet, how much these developments in new acceleration techniques, will help to reduce the costs.

Conclusions and outlook

A brief overview of the most well known developments in accelerator technology has been presented in the context of a potential cost reduction of accelerators in PT. Several options seem to be possible, but more dramatic changes are needed for a major cost reduction. And, since experience has shown, that major steps in PT need approximately ten years from first trials to introduction into the clinic, it is expected that a dramatic, say 50%, cost reduction of PT will not be reached in the near future.

Apart from the possible lower costs, it is important to consider the effect of the new techniques on the treatment possibilities. For each new technology, it should be verified whether the dose distribution delivered provides comparable quality to that currently available in PT. Compromises taken to reduce the cost should not be accepted when this cannot be guaranteed. For the time being, the higher quality of the proton treatments is the only important reason to be competitive to other treatments. Accelerator related properties like intensity, pencil-beam size, energy spectrum, stability, reproducibility, time structure and the time needed to change a parameter, are the most relevant to consider in this respect.

Nevertheless, already now many successful developments in accelerator technology are available in commercially available facilities. Some of these are focusing on the lower initial investments when acquiring a PT facility with only one treatment room. Single-room facilities will offer opportunities in certain cases, but it is not clear in general, whether single-room facilities will make with PT treatments cheaper.

At present it is encouraging to see, that accelerator developments, such as smaller accelerators, facility size reduction and faster treatments, are entering into clinical facilities and are contributing to a reduction of the treatment costs. Next steps in cost reduction can only be achieved with further research in accelerator physics.

3. Technology for delivery efficiency

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Introduction

The spatial distribution of a beam from a particle accelerator is not normally a conformal match for the desired target. Therefore, one must direct the beam trajectory and 'spread out' the beam transversely and longitudinally (in depth). In doing so, one attempts to optimize the three-dimensional distribution and in some cases a four-dimensional (4D) distribution, the latter including the time dependence of beam delivery relative to patient motion (see article on '4D planning and delivery'). A key goal is to deliver a physical dose distribution consistent with a predetermined treatment plan. This treatment plan includes specifying the direction that this spread out beam should enter the patient.

For decades the main delivery modality was that of beam scattering (Koehler *et al* 1977). This is accomplished by scattering the beam with various types of physical devices in the path of the beam. Sometimes this is done passively enabling the entire volume of the dose to be delivered instantaneously and in some cases it has more dynamic elements such has range modulator wheels and beam current modulation, which can deliver the full volumetric dose in a fraction of a second. The beam delivery modality which has evolved to be the more desired and soon-to-be the most prevalent is that of beam scanning (Pedroni *et al* 1995) wherein the unmodified accelerator beam distribution is transversely scanned magnetically and the beam range is controlled by modifying the beam energy both of which have a finite time dependence. This beam was originally delivered from a fixed angle beamline, but then proton and heavy ion gantries were developed. These added needed (at the time) flexibility in beam direction as well as considerable expense.

For the purposes of this section, the word 'efficiency' is interpreted to mean efficient in cost, time and treatment efficacy.

Status

Most of the modern facilities are designed to use particle beam scanning with rotating gantries. Most have been constructed to deliver a dose rate of about 2 Gy per liter in a minute. Scanning beams hold the promise to deliver the most conformal physical dose distribution, however the ultimate dose distribution possible according to the laws of physics is still not achieved as a result of certain constraints and limitations. Recently, different beam delivery methods are being re-explored, such as mini-beam ribbon (Peucelle *et al* 2015) and FLASH (Mazal *et al* 2020) (see article on 'Treatment planning') irradiation. These modalities may require revised beam delivery parameters including much higher dose rates.

Current and future challenges

This chapter focuses on the system components used to direct the beam to the patient including the beam spreading technology and the gantry. The challenges to be addressed here are specific to these components. Elsewhere, issues of localization and stopping power uncertainties will be addressed. Given the current beam delivery implementations, the necessity to address organ motion results in applying methods that include: Gating, Repainting and Beam size adjustment. The current systems are capable of these techniques. However, their design may be constrained to avoid the fundamental issues that would address the key challenges of the future. These challenges include:

- Reduced system cost, and
- Faster, accurate and safe beam delivery

The beam scanning delivery technology involves informing the system of the desired location and dose to be delivered in real time. If one knew precisely where the target was at any given time, the equipment technology is capable of producing and delivering a beam to that location. However, treatment planning has not yet reached the capability to calculate and transfer real time adaptive plans based upon the dose delivered with real time imaging (see articles on 'Treatment planning', '4D planning and delivery' and 'Adaptive Therapy'). Therefore, one would first consider pre-planned delivery options.

Delivering a 3D dose distribution in a time period small compared to organ motion would be a fundamental solution to handle the organ motion challenge. Currently, on the average, it takes on the order of a minute to deliver the volumetric dose required by the treatment plan (see article on 'Delivery Technology'). This is comprised of two seconds or less to change the beam energy, each time it is required, and the time to paint a given range layer which is about, on the average, a second. Therefore, 30 layers will take about a minute. Some facilities are capable of faster delivery, such as 0.1 seconds to change energy. However even that amounts to more

than 3 seconds total for just the energy changes, not short compared to the period of organ motion (respiratory or cardiac). Scanning dipoles exist with the capability of moving the beam at frequencies of 100 Hz (although the slowest ones move at 3 Hz), and for spot scanning the settling time of the magnet/power supply combination can be as large as 5 msec per spot (which, for 40 $\times$ 40 spots, could result in a 'dead-time' of about 8 seconds per layer). Furthermore, FLASH beam delivery requires dose rates of $>$40 Gy s^{-1}. It's not exactly clear what the beam delivery implications will be for this technique. Is that dose rate in the distal layer only sufficient, or is it required for the full volume and is there a time dependence, as in painting the volume, to the effect? Another aspect of this challenge of increasing the speed of the beam delivery are the commensurate issues of accuracy and safety in delivering the beam. One expects a dose delivery accuracy of better than 2%. Currently ionization chambers (IC) are predominately used (in fact they are legally required in most countries). These systems may take 100 usec, on the average, to detect and record the dose delivered. Therefore, there is always a delay and it is essential that the dose rate is such that the dose tolerance should not be exceeded in the time it takes to detect it. This results in a limitation of the beam current to fractions of a nano Ampere and results in dose rates that are currently used. To increase the speed of the scan or beam delivery current a factor of 60–100, to address organ motion, or a lot more (for FLASH) would require advances in the technology. The challenges identified so far include:

- Speed of Scan
- Speed of ICs
- Speed of Energy Change

When considering the cost of a particle therapy facility one cannot compromise on safety. One desires to deliver the beam to the appropriate target location in a speed consistent with the target accuracy desired. One of the most expensive pieces of equipment in a particle facility is a gantry. The size, weight, fabrication and building structure for such a piece of equipment is probably the single largest expense in the facility. Attempts to reduce the cost of this component include shrinking its size longitudinally (via superconducting magnets (Gerbershagen *et al* 2016) or corkscrew geometry (Koehler 1987), or reducing the lateral extent by limiting the rotation range to about 180 deg (Pedroni *et al* 2004). However, while the superconducting option can reduce the cost of these systems for heavier Ion facilities, it does not reduce the facility size significantly for proton centers. The largest cost reduction would come from the elimination of the gantry mechanical component.

Advances needed to meet the challenges

If one looks again at the key challenges, perhaps one can identify the most appropriate way to address them, given what is known now or can be imagined now.

Speed of scan. Conventional magnets exist that can move the beam quite rapidly. The issue is how big they need to be, which is related to the size of the field extent and the distance from the magnets to the target. Without a gantry (solving two problems with one solution) the distance can potentially be larger and the magnets smaller, with lower inductance enabling reduced dead time and faster current changes. However the dose rate must be sufficient to deposit the desired dose in the time, and while most accelerators can do this, the existing ICs used cannot.

Speed of ionization chambers. Smaller gap, higher voltage systems are required, which may be possible since the scanning beam modality requires lower beam current than was necessary in the scattering systems. Or perhaps one can replace these with alternative options. For example, knowledge of the beam's incoming trajectory together with the magnetic field should be capable of accurately predicting the position of the beam on target, thereby avoiding the need for additional redundant instruments such as Ionization chambers. Other instruments for counting charge such as toroids or scintillators might be considered to replace ionization chamber dose monitors. This may necessitate modification of the regulations.

Speed of energy change. This is perhaps the most technologically difficult issue. The contributions to this time include the accelerator (for some systems) and the beam line. Synchrotrons are now starting to use 'multi-energy' extraction (Younkin *et al* 2018), and cyclotrons rely on a degrader with the magnetic energy analysis system. One method is to eliminate a beam line (Prusator *et al* 2017), which is possible for a single room system. Otherwise the magnetic beam line system must be designed to enable faster energy changes (e.g. on the order of 0.02 s). This is possible from an engineering point of view, but may increase the system costs and commissioning complexity. Feedback and feed-forward systems are possible, some examples of which have been implemented.

System cost. The simple, and yet not widely accepted answer is to eliminate the gantry. With decades of experience using gantries, given the convenience of setting the beam trajectory and patient positioning, it is hard to conceive of this disruptive change. Prior to gantries one used fixed beam lines for treatment and experienced difficulty in achieving the desired beam angles relative to the patient orientation. However, one needs to consider the modern systems, with scanning beams, robotic positioners, more flexible imaging and flexible immobilization. Scanning beams are highly conformal, and that means that they are capable of delivering a conformal dose with fewer and more limited field angles. Studies have shown that fewer non-coplanar field geometries are necessary (Yan *et al* 2016). The issue is then what is the range of patient orientations that are necessary and how to ensure that the patient anatomy is in the appropriate position for these geometries? Robotic positioners can orient the patient in flexible positions (upright, lying down and forms of sitting) and in-room imaging is capable of verifying a patient's position in multiple orientations, if that is needed in the course of one fraction (e.g. orientable CTs, swing arm CBCTs). Comfortable and easy to use immobilization is perhaps the element most lagging in this equation. Developments of this are underway.

Concluding remarks

The evolution of beam delivery technology is sometimes done adiabatically. While the change from scattering to scanning was, in fact, a disruptive technology, the former has slowed the evolution of the latter. Sometimes one has to identify the issues very clearly and boil them down to their essence to, in this case, realize that one needs to use an appropriate imaging technology and immobilization to enable a gantry-less solution and deliver a beam very quickly. These are the technologies that will deliver the largest gain. Probably the most important development to achieve these goals is improved beam instrumentation, or a revisiting of the type of instrumentation that is required. Perhaps it may be noted that there is another goal relevant to beam delivery technology, which at first thought may appear separate from the considerations identified above, but upon further reflection may become the magic bullet of radiotherapy. If this 'FLASH' radiotherapy turns out to be shown to be favorable in humans, then the imperative to address the fast dose delivery with charged particle imaging will enable further significant reduction of side effects to healthy tissue while enabling delivery of the dose in a time scale short compared to motion and delivered to the correct location and depth as given by direct charged particle imaging. It is critical to direct the evolution of the technology to address the current challenges and finally achieve what charged particle therapy has ultimately promised for the past half century. And this can all be done with less expense if one removed the rotating gantry.

4. Delivery technology

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Status

One of the areas where a significant cost reduction in PT seems possible and achievable is in the potential of increased efficiency (see article on 'Efficient Treatment Room Utilization'). As today, the allotted treatment times are typically significantly longer in PT than in conventional, linac-based treatments (Suzuki *et al* 2016).

There are many reasons for the longer treatment times in PT, e.g. on average more complicated treatments with several fields with/without the use of range shifter, a higher need for imaging due to the need for rapid adaption and the sharing of the accelerator with several treatment rooms. Despite the increasing installations of 'single room' solutions in recent years, multi-room facilities with anything from two to five rooms still dominate. Sharing the beam means that one or two (or even three) rooms may be before you in line when you are ready to treat. A slow field delivery time hence also affects all those rooms waiting for the beam and any second gained by faster beam delivery will be multiplied by the number of rooms waiting. Waiting time may also deteriorate the treatment since the patient may move during this period and call for additional imaging or position verification. The cost for a treatment, or fraction, scales more or less linearly with the time the patient spends in the treatment room and reducing the length of the time slot, without compromising the quality of the treatment, will consequently reduce the cost to the same extent.

Advances in technology to meet challenges

Looking deeper into the technological solutions for spot scanning facilities today, one easily gets the impression that the concept of treatment efficiency has largely been neglected in the design process. The different accelerator types (cyclotrons, synchrotrons and synchrocyclotrons (see article on 'Accelerator Technology') all have different characteristics and will therefore in the following be partly treated separately, although the main focus will be on (isochronous) cyclotrons, since it is the most used type of accelerator in PT.

There are three main parameter ruling the time it takes to deliver a given treatment field; the spot delivering time, the time between spots and the time it takes to change the energy (see article on 'Technology for delivery efficiency'). A cyclotron produces a continuous beam (ignoring the RF frequency pulses) and to deliver a spot with a given number of protons (or MU's), the beam is turned on, the dose is monitored by a dose monitor and turned off when the pre-set value is approached. This means that the signal from the monitor chamber must be tracked and analyzed in real-time and to achieve a high degree of accuracy, a certain time, typically a few ms, is needed. Prior to irradiation, an estimate of the needed beam current is done by the system to ensure the spot duration not being too short. With faster electronics and analytical capacity, this could probably be somewhat reduced in the future. However, and more importantly, the possibility to adjust the beam current from the accelerator *between* consecutive spots is of crucial importance. In some systems this can be done, meaning that all spots have (more or less) the same duration of a few ms, whereas in other systems, the beam current is calculated to ensure that the smallest spot (with the smallest number of MU's) will be long enough, and the modulation of the spot intensity over each energy layer, is done by prolonging the spot duration with the same beam current. In the latter case, the time to deliver a field will typically be at least twice as long, as if the beam current was modulated (Müller and Wilkens 2016). The actual prolongation depends on the amount of modulation the spots in the field have and on the minimum number of MU's allowed, but it's important to realize that even in single field optimized treatments, there is a significant spot modulation, also within each energy layer.

In a synchrotron, the situation is similar in this respect. The accelerator is loaded with a certain number of protons and then the protons are extracted in 'spills' and the accelerator is filled up again. During a spill, the beam can be viewed as continuous and the same principles as for a cyclotron can be applied.

A synchrocyclotron represents a completely different situation. Here the beam is pulsed with a beam duration of only a few μs per pulse, pretty much like in a linac. Hence, the pulse duration itself does not really contribute to the beam delivery time, but since the number of protons (or MU's) delivered in a pulse is ruled by the upfront loading of the cyclotron, rather than by the reading of the monitor chamber, more than one pulse is needed to build up a spot. This is due to the fact that the number of protons in a pulse cannot be predicted (or determined) at the ion source level to the accuracy needed in PT. The important factor that rules the actual beam delivery efficiency then becomes the pulse repetition frequency (PRF), which scales more or less linearly with the efficiency. For the present and most widely spread synchrocyclotrons, the PRF is between 500 and 1000 Hz; increasing the PRF will directly reduce the beam delivery time.

The second parameter determining the beam delivery time is the time between spots; the time it takes to move from one spot position to the next. This is mainly governed by the speed of the scanning magnets. When the magnetic field is to be changed in an electromagnet, eddy currents generated in the yoke of the magnet reduces the speed of which this change can be done. A way to counteract this effect is just to wait until the magnetic field has settled and stabilized. If this time is to be reduced, an approach could be to predict the spot position effect due to this and compensate for that, and in that way allow a reduced settling time (Psoroulas *et al* 2018). Another method is to introduce 'line-scanning'. With this approach the pencil beam is continuously moved in lines over the area to cover. Modulation of the beam intensity can either be made by modulating the beam current, or by keeping the current constant but modulating the speed of the scanning magnets, or both (Klimpki *et al* 2017). A prerequisite is that the beam current is stable enough and this may present a challenge for synchrotron-based systems. This method can be made significantly faster and solves, at least to some extent, both the problem of spot duration and the dead time between spots, but is demanding in terms of beam delivery monitoring and validation. To perform line scanning, a continuous, rather than pulsed beam, is needed. Hence, line scanning cannot be performed with a synchrocyclotron.

The third parameter is the time it takes to change the energy from one layer of spots to the next. For most modern cyclotron based systems, this time is around one second, or slightly more. Large efforts have been done to reduce this at some centers, e.g. at the Paul Scherrer Institute in Switzerland (Klimpki *et al* 2018). The main purpose of this is to better manage organ motion and e.g. to make volumetric re-painting feasible, but without doubt, this parameter also influences the overall efficiency.

In synchrotrons, each energy layer typically demands a spill of its own. This means that even if the number of spots within a certain energy layer is small, the accelerator has to go through the whole acceleration cycle, which takes typically several seconds. For details of the timing of synchrotrons in a clinical context, see e.g. Boria *et al* (2018), Gelover *et al* (2019). Ways to improve this has been done by e.g. by decelerating the beam during a spill (Iwata *et al* 2010, Younkin *et al* 2018) and with the so-called multiple energy extraction method, beam delivery time can be reduced by a third for typical clinical fields. Another approach to speed this up can be to decrease the 'dead time' between the spills by increasing the ramping speed of the magnets (Trbojevic *et al* 2011).

Once a PT system is installed, most of the above parameters are given and cannot (easily) be improved or changed. If the time to deliver a spot and to move to the next position cannot be changed, the actual number of spots in a given energy layer can (van de Water *et al* 2019). Larger spots mean that larger distance between spots can be applied, and hence fewer spots can be used without causing a dose ripple (for further relevance of this, see also article on 'Treatment planning for pencil beam scanning PT'). Fewer spots with a larger number of protons in each spot, is associated with significantly reduced beam delivery time. The exact reduction is dependent on several parameters such as available beam current and is also different between different delivery systems. Several PT vendors offer different 'spot ID's' by the introduction of a scattering foil in the treatment head (nozzle). The price to pay for larger spots is a larger penumbra and somewhat reduced modulation possibilities and consequently this approach has not become a standard tool in most clinics. A way to overcome this would be to allow different spot sizes within the same energy layer, e.g. smaller spots at the edges and larger spots in the central part of the field. To make this possible, rapid changes of the spot sizes are needed which is difficult with a scattering foil. With present systems the foil is either in or out during the complete field. Attempts to widen the beam with magnetic defocussing instead of a scattering foil have been explored but is not widely available. However, such an approach would also have the appealing quality of designing the actual spot size individually for each energy, which cannot be done with a limited number of scattering foils. Yet another approach to solve the penumbra drawbacks of larger spots is to combine the scanning with a collimator. Advanced solutions are required in order not to detract the other obvious advantages with the spot scanning technology. One such commercially available solution is the so-called Hyperscan from Mevion (Kang *et al* 2018).

The equivalent of spot size in the depth direction is the initial energy spread of the proton beam. Typically this is around 1%, resulting in a very steep distal fall off of the Bragg peak. Although this is often seen as an advantage with PT, the sharpness of the peak may be too sharp, in particular at the low energies, to be clinically useful (considering e.g. range uncertainties) and results in very small energy steps and many energy layers to avoid a dose ripple. One way to intentionally introduce an increased energy spread and hence soften the Bragg peak is to apply a ridge (or ripple) filter (Grevillot *et al* 2015, Printz Ringbæk *et al* 2017). With a proper design, virtually any shape of the Bragg peak can be obtained. But just as with scattering foils to broadening the spots, a ripple filter is yet another mechanical device to be introduced into the beam line, typically by manual handling, with limited possibilities to change between energy layer or, even more so, from one spot to another. If the gantries could be designed with a wider momentum spread acceptance, the energy spread could be determined further up-stream in the beam line and in cyclotrons there are already a momentum slit in the energy selection system that could be used for this purpose (Hsi *et al* 2009, Nesteruk *et al* 2019). But again, the actual acceptance of the beam line is given by the original optical design and cannot (easily) be retro changed. The longer it takes to change the energy of the proton beam, the more important it gets to optimize the number of energy layers used. This aspect can be

introduced in the treatment planning optimizer and significant energy efficiency gains have been demonstrated (Kang *et al* 2008, Cao *et al* 2014, van de Water *et al* 2015). An exception to the above situation is the gantry-mounted design by Mevion where no energy selection is present and the sharpness (or lack thereof) is the same independently of energy.

In conventional radiotherapy, the move from IMRT to volumetric modulated arc therapy (VMAT), led to a significant efficiency gain. A similar development has been demonstrated also for PT (Li *et al* 2019a, 2019b), but since the difference in dose distributions are greater than in the photon case, it is probably too early to know if proton arc therapy will become a standard delivery tool in the future. In IMRT a relatively large number of fields are typically used, meaning that the dose is distributed to larger volumes. This effect is even larger in VMAT, yet smaller than the difference is between IMPT (where relatively few fields are used) and PT arc therapy.

This far the beam delivery time has been discussed. Obviously, the beam-on time is just a small part of the overall 'patient-in-the-room' time and an increased 'dose rate' may only have a limited effect on the overall efficiency. But for many of the systems a reduction by a factor of two or more for the beam delivery time seems realistic and for multi room systems, this could result in an improved efficiency of the order of 10%–25%. If complex beam delivery applications are used, e.g. re-painting or gating for motion mitigation, the efficiency gain is even higher.

As mentioned above, a faster beam delivery time will have the greatest impact on multi room facilities, where the waiting time for the beam is an obvious limitation (see article on 'Efficient Treatment Room Utilization'). But also the beam sharing system itself is of importance. Most systems have the possibility to choose a 'priority' for their treatment, i.e. to choose whether or not to give the beam away between consecutive fields of a patient. To accept to give the beam away reduces the waiting period each time, but increases the number of room switches and increases the overall treatment time. Faster room switching, e.g. by allowing dedicated power-supplies to each gantry-specific magnetic component, rather than sharing those, and smarter scheduling tools, might reduce the problem. Future design improvements with the possibility to share the beam, i.e. deliver beam to more than one room at the time, may be possible, but this is technically complicated and will lead to increased equipment costs (Schippers and Lomax 2011).

IG (see article on 'IG') is used extensively in PT and this obviously slows down the efficiency. One cannot argue for reduced IG as long as it improves the quality of the treatment leading to improved clinical outcome. However, IG in PT is often to a substantial part also used as a technical quality control to make sure the equipment, in particular the robotic patient positioner, is in the right position, rather than checking the positioning of the patient or the target. Poor accuracy and precision of the patient couches is still a problem and limited trust in the equipment leads to over-imaging and prolonged treatment sessions.

Manual handling of beam modifying devices, in particular range shifters constitutes a substantial source of inefficiency, in particular for installations where the range shifter cannot be remotely operated. To counteract this source of treatment prolongation, it is not uncommon with a sub-optimal use of the range shifter, e.g. to use it for all fields, even those where it's not needed, just to avoid the delay of manual handling, but with a deterioration of quality. Improved penumbra and better dose distributions can sometimes be achieved by splitting the fields and use the range shifter only for the energy layers it's really needed, but to apply this method in an efficient way, automation is needed (Fracchiolla *et al* 2019). Remotely operated range shifters are urgently called for and it should not be an unsolvable issue also for existing clinics.

As discussed in a previous chapter (see article on 'Technology for delivery efficiency'), gantries in PT constitutes a significant part of the investment. The gantries in PT are substantially larger and heavier than conventional gantries. As a consequence, and for safety reasons the gantry speed is sometimes limited compared to the 1 RPM commonly encountered in conventional radiotherapy. Some systems also experience a 'cork screw effect', meaning that the exact position of the gantry is depending on the direction from which the position is approached, i.e. clockwise or counter-clockwise. For some systems an 'over-travel' is needed if the gantry is rotated from the wrong direction, meaning a further prolongation of the treatment session. The issue of heavy gantries may not be trivial to fix for existing gantries, but should be a parameter to consider when procuring a PT system. The over-travel issue, however, is expected to be solvable.

Concluding remarks

There are a number of reasons why PT is so much slower than conventional radiotherapy. To a significant degree this could be improved in future designs by ensuring a faster beam delivery time, faster and more reliable gantry designs and maybe even by the possibility to share the beam in a smarter way in multi room facilities. For existing facilities, the options are limited when it comes to the beam delivery technology, but there are some obvious issues that should be promoted, e.g. remotely controlled range shifters, the possibility to modulate the beam current in-between consecutive spots and multiple energy extraction for synchrotrons.

5. Efficient treatment room utilization

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Status

Efficient utilization the Particle Treatment room for patient treatments and QA will reduce the overall cost of treatments and improve patient care. The overall financial impact of a facility is not only the upfront equipment and building expense, but in the long run it will be efficiency of daily patient treatment and room occupancy that dictates true cost of operation and patient treatment cost. In this section, we will assume sufficient demand to fully occupy a given facility; therefore, details and method of effective demand generation will not be discussed here but is a crucial concept in cost reduction.

There are four main time components for patient occupancy in the treatment room: (1) patient and therapist entering and exiting the treatment room; (2) immobilization and image guided localization; (3) beam on time; (4) equipment preparation (gantry and table rotations and beamline settings). The other major room occupancy is the QA procedures that must be conducted. This includes daily, monthly, annual machine QA and patient specific QA (PSQA).

The current status for room patient room occupancy is as follows: (1) 4–5 min to enter and 4–5 min to exit the treatment room; (2) 4–5 min for immobilization and 3–5 min for IG; (3) 2–3 min of beam on time; (4) 3–6 min for gantry rotation and beamline settings. This gives a total of approximately 20–30 min, which is currently difficult to achieve in most centers. These are just approximations, as some treatment sites may take longer. Many current proton facilities reserve 20–45 min time slots for the average patient, while most photon facilities reserve only 15 min time slots, this incudes facilities with have both proton and photon capabilities.

Current and future challenges

Current challenges include the fact that particle therapy is particularly sensitive to small anatomical changes, which can erode the quality of the target coverage and normal tissue sparing (see article on 'Uncertainties'). This makes the immobilization and IG step extremely crucial (see article on 'IG'). A lot of time is spent in the IG step, as the data provided is not always fully informative as to the acceptability of the current patient setup. For example, if the IG currently shows partial sinus filing in a head and neck plan that had none during simulation, what is the compromise, if any, to the target coverage and/or normal tissue sparing? These types of changes are difficult, if not impossible, to account for with robust optimization planning techniques.

In the future, many treatment sites will move toward hypo-fractionation and/or incorporating some type of target motion mitigation technique to reduce the interplay effect (under or over dosing due to beam scanning motion relative to breathing motion). As these trends continue, the limitation in effective dose rate will become more pronounced. The current dose rate standard is approximately 1–2 Gy min^{-1} to a cubic target with a one liter volume; however, this dose rate is difficult to achieve with real targets. This limitation is mainly due to energy layer switching time, spot scanning time, and effective particle current at lower energies. For multi-room facilities is the additional limitation due to a finite field or course or room switching time. A typical room switching time is 20–45 s, given 120 fields a day and 30 s switching time this is an hour per treatment room that is 'wasted'. The interrelationship between treatment room numbers, switching time, and setup time have been examined, however each system has unique parameters that make true generalization challenging (Fava *et al* 2012 and Bolsi *et al* 2008).

The increase in hypo-fractionation will also increase the number of PSQA as the expectation will be to treat more patients in a given month and hence increase the PSQA workload. The current practice for PSQA in many centers is time consuming and with no change in efficiency will limit the total number of new patient starts in a given month.

Advances in technology to meet challenges

Many centers are beginning to adopt a log based/machine files approach to PSQA (Belosi *et al* 2017 and Johnson *et al* 2019). This is a first step to decreasing the amount of time the treatment room is utilized for PSQA and thereby freeing up more time for patient treatments. Specifically, a log based QA approach uses the data from the treatment delivery system to ensure proper delivery of the radiation. The cited references detail how this is done and quantifies the time savings. Another practice currently being implemented in some clinics is the use of direct shield doors. These doors open quickly and eliminate the need for a long maze; thereby reducing the time needed for patients and therapist to enter and exit the treatment room. While implementing advanced IGRT such as high quality CBCT is crucial, the particle gantry rotation speed remains an issue. Work is currently being

done to increase the gantry rotation speed to from ½ rotations per minute (RPM) to 1 RPM. Other proposals suggest a closed design such that the 1 RPM restriction will no longer be an issue issue (similar to a TomoTherapy design). Research and development is also underway to improve the effective clinical dose rate. This will not only reduce treatment time, but may allow for minimization of the interplay effect. The goal is to allow a stereotactic field of ~200 cc to be delivered within one small breath-hold, ~5 s. Accelerators such as the VEMIC (Hori *et al* 2019) would allow high dose rates at all energies without the use of an energy degrading device. The time required for beamline settings, particularly in a multi-treatment room with one accelerator setup is being addressed twofold: first by having one accelerator support only one treatment room, and two by optimizing the time required to reset the beamline from room to room for multi-room systems.

In addition to the mechanical and control system improvements described above, much advancement is needed in the treatment planning realm. One method the treatment planning can aid in treatment room utilization is by optimizing the spot pattern to reduce the overall treatment delivery (see also articles on 'Delivery Technology' and 'Treatment planning'). However, the key improvement will be the realization of Real-Time Adaptive Therapy, which will require Real-Time PSQA that does not need to occupy any treatment room time and is transparent to the end user. Particle therapy is, in general, more sensitive to setup and anatomical differences than is photon therapy (see article on 'Uncertainties'). This sensitivity increases the time used during setup and IG. The use of efficient Real-Time Adaptive Therapy (see article on 'Adaptive Therapy') can lead to decreased room time and increased dosimetric plan quality.

Concluding remarks

As we can see from the previous section, there is no reason that in the near future we cannot have efficient treatment room utilization for both patient treatments and QA that will enable the cost of therapy to decrease while simultaneously increasing the quality and effectiveness of the delivered treatments. These advancements in technology are either currently being implemented in select clinics or are on the roadmaps of different vendors and/or facilities. The relative weight of each item to the efficiency gains is hard to assess as it depends on the details of the individual system, but these are items to consider and do a thorough investigation on when designing a future system. With these advancements, there is no reason that a patient time slot cannot be 15 min or less, similar to most current photon treatments.

Part 2: Improving planning and delivery

6. Uncertainly precise—uncertainties in PT and how to tackle them

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Introduction

Uncertainties are an inherent part of the radiotherapy process, but have been particularly highlighted in PT. Indeed, there is hardly a conference or workshop in this field where 'robustness' (the corollary of uncertainty), in the form of tools for its evaluation or optimization, is not a hotly discussed topic. In many ways, this is a very healthy development. On the other hand, are we in the community really putting our resources in understanding the most clinically relevant uncertainties? In this brief article, we will identify fourteen sources of uncertainties in the whole process of PT, each one identified by a roman numeral. Based on this, we will propose a list of uncertainty issues that should be addressed in particle therapy in the next years, together with an estimate of their relative clinical relevance. These are summarized in table 1. Note, that the categorization and estimates of clinical relevance in the table, and indeed throughout this short article, are necessarily based on a very personal view which some may find controversial. As such, the author does not expect that all readers agree with the views expressed here. But I do hope that the sometimes provocative statements promote some debate.

Current and future challenges

Clinical uncertainties. Uncertainty raises its ugly head already at the time of diagnosis (or the missed diagnosis) of cancer (**I**). But even once a tumor is identified, it cannot always be stated with certainty what the histology of the tumor is, or even more, its stage of advancement and spread (**II**). Nevertheless, all these factors will have a substantial impact on the management of the disease, which from the point of view of radiotherapy means the definition of the total doses and fractionation scheme with which the tumor should be treated, as well as the size and form of the expected microscopic spread of the disease. Indeed, this delineation step has been well documented to be haunted by huge uncertainties and inter-clinician variability (Aznar *et al* 2017, Apolle *et al* 2019, Mercieca *et al* 2020) with the contours for the *same patient* varying by typically 3 cm (Hausdorf distances) for some indications (**III**).

Biological uncertainties. At the most fundamental level, the above-mentioned clinical uncertainties are related to the underlying biology of the patient, their normal tissues and the tumor. In addition however, there are substantial uncertainties in the biological *response to radiation* of the patient and tumor (see article on 'Biomarkers').

Perhaps, and as discussed in an accompanying roadmap article on the RBE in this issue, the largest biological uncertainty is due to the inherent variation in individual sensitivity of patients to radiation (**IV**). In addition, there is considerable uncertainty in dose response at the cellular level, as typically characterized by the Linear-quadratic model. For this, tissue specific alpha-beta values are notoriously difficult to determine *in vivo*, and even the model itself is likely a gross simplification of the complex mechanisms of radiation damage at the cellular and organ scale (**V**) (Unkel *et al* 2016, Nagle *et al* 2018). Finally, and perhaps the most clinically relevant biological uncertainties, is our current lack of knowledge of the clinical response of tumors and organs to inhomogeneous dose distributions (**VI**).

All of the above are common to all forms of radiation therapy. For particles however, there is the additional uncertainty of their differential biological effect, typically characterized as an RBE. The variability of this is covered elsewhere in this issue, but in addition, there is mounting evidence that the fundamental differences of DNA damage by particles will lead to effects more complex than can be encapsulated in a simple relative value (**VII**) (Grosse *et al* 2014). Much still needs to be understood in this respect that could substantially affect how particles will be exploited in the future.

Positioning and anatomical uncertainties. Positioning and anatomical uncertainties are present for both photon and proton treatments. However, particularly for anatomical changes, proton treatments are significantly more sensitive to such changes than in conventional therapy. For instance, in addition to potentially deforming the tumor and surrounding normal tissues, more importantly for PT, they can significantly affect particle range in the patient. Indeed, for many anatomical regions, uncertainties in the accuracy and precision of proton treatments resulting from time dependent changes of the patient

Table 1. A categorized list of uncertainties, together with a personal ranking of their relative clinical relevance. 5 is most relevant and 1 least relevant. Proton specific uncertainties are highlighted in italics.

Uncertainty category	Source of uncertainty	Relative clinical relevance	Example research areas for uncertainty mitigation
I	Tumor diagnosis	5	• Improved physiological, functional and cellular imaging
II	Tumor staging	5	• Tumor specific bio-markers
III	Tumor extent	4	• Improved physiological, functional and cellular imaging • AI/ML supported automatic contouring
IV	Patient specific sensitivity	4	• Radio-sensitivity assays
V	Cellular response to radiation	4	• Pre-clinical *in vitro* studies
VI	Organ response to radiation	4	• Organoid and small animal irradiations • Curative irradiation of spontaneous tumors in medium size animals • Multi-variate outcomes analysis
VII	*Differential biology—protons/x-rays*	*3*	• *Beyond RBE pre-clinical cell and small animal studies* • *Multi-variate outcomes analysis*
VIII	*Inter-fractional anatomical changes*	*3*	• *Proton compatible on-board imaging* • *Fast and automated plan adaption*
IX	*Cyclical intra-fractional changes*	*3*	• *Near real-time, on-board, 2/3D imaging* • *Gating/Breath-hold/re-scanning* • *Ultra-fast delivery*
X	*Systematic intra-fractional changes*	*3*	• *Near real-time, on-board, 2/3D imaging* • *Fast and automated plan adaption* • *Ultra-fast delivery*
XI	*Patient positioning*	*2*	• *Comprehensive robust planning* • *Fast and automated plan adaption*
XII	*Residual range uncertainties*	*2*	• *Dual energy/Photon counting CT* • *Proton CT* • *In vivo range verification* • *Comprehensive robust planning*
XIII	*Dose calculations*	*2*	• *GPU accelerated Monte Carlo*
XIV	*Machine delivery*	*1*	• *Improved position and dose monitoring* • *Faster monitoring, electronics and processing*

themselves can be huge, and substantially larger than many other uncertainties (see e.g. Albertini *et al* 2008, Hoffmann *et al* 2017 and Nenoff *et al* 2020).

Such changes can occur either between (inter) or within (intra) fractions. For some inter-fractional anatomical changes, for example variable filling of internal cavities, weight loss/gain or tumor shrinkage/growth, substantial changes to target coverage can result (**VIII**) (Albertini *et al* 2008, Hoffmann *et al* 2017). *Intra-fraction* motion adds to this uncertainty cocktail, with both cyclical motions (e.g. breathing, heart beats etc) (**IX**) (Grassberger *et al* 2013), as well as slower time-scale drifts of the patient anatomy and/or tumor (base-line shifts) (**X**) adding considerable uncertainty to the treatment (see article on '4D planning and delivery').

Delivery uncertainty will also occur due to the inevitable inaccuracy with which a patient can be positioned in relation to the treatment beam on a day-to-day basis (**XI**). This is a well documented problem, with many proposed solutions already available, ranging from the use of the statistically calculated planning target volume (PTV) concept, through to plan optimization that also incorporates multiple set-up uncertainty scenarios (Unkelbach *et al* 2018).

Imaging uncertainties. Even without anatomical and set-up variations, there will always be an inevitable 'base-line' of uncertainty of the range of particles in the patient, simply due to the indirect imaging processes currently used for estimating *in vivo* range (**XII**) (see article on 'Imaging for treatment planning'). For example, single-energy x-ray CT has been predominantly used for calculating proton range in the patient. In the community,

such an approach is estimated to have an uncertainty of ±3%–3.5% (Paganetti 2012), although this will be lower in most soft-tissues, whilst being somewhat higher in some forms of hard bone. The introduction of dual-energy CT (DECT) has now decreased this to about the ±2% level (Wohlfahrt and Richter 2020). In the presence of non-biological implants such as metal teeth fillings and surgical stabilizations however, range uncertainties can be locally much larger, due to artifacts resulting from limitations in the image reconstruction processes when high-density materials are present.

Dose calculation uncertainties. Despite having sophisticated tools for designing, simulating and evaluating treatments either before (in the treatment planning process) or after (for outcomes analysis) treatment, the accuracy with which such systems can predict the point-to-point dose within the patient are limited, even if all the other patient related uncertainties are ignored (**XIII**). Although MC calculations are undoubtedly more accurate than analytical approaches, and will become increasingly useful as calculation times reduce (Qin *et al* 2016, Schiavi *et al* 2017, Ma *et al* 2018), their accuracy is ultimately limited by how well the patient anatomy is represented by the CT on which dose is calculated (see *Positioning and Anatomical Uncertainties* above).

Machine delivery uncertainties. The final category of uncertainties considered here are those of the delivery machine (**XIV**). Briefly put, uncertainties in machine delivery are negligible in relation to the other uncertainties affecting fractionated particle therapy, at least if monitored and pro-actively corrected as part of a comprehensive QA program. Nevertheless, there are undoubtedly areas for improvements in machine design and technology that can help to reduce patient related uncertainties, such as improved on-board imaging to help mitigate inter-fractional patient changes, as well as substantially reduced delivery times to mitigate the effect and magnitude of intra-fractional motions.

Advances in technology to meet challenges

An overview off all the categories of uncertainties discussed above is shown in table 1, with a relative indication of the clinical relevance of each. Note, that this scale is not meant to be linear, and is also not meant to indicate that any area of research to mitigate these uncertainties is necessarily more important than any other. It just aims to put the uncertainties discussed here into clinical context. In addition, possible research topics for mitigating the categorized uncertainties are listed in the right-most column, with those where the solutions will be PT specific highlighted in italics. As such, this table aims to provide a research and development roadmap for comprehensively reducing uncertainties in PT. If successfully completed, these will substantially improve the quality and efficacy of what is an already a precise and successful treatment modality.

Concluding remarks

There are uncertainties related to every step of the PT process, and eliminating them completely is impossible. However, through technological and methodological developments, improvements can be, and should be, made everywhere in an attempt to systematically reduce the uncertainty budget of PT.

7. Treatment planning for pencil beam scanning PT

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Status

If the delivery machine is the heart of radiotherapy, then treatment planning is the brain. Whatever the capabilities of the beam delivery system, these can only be exploited to their clinical best by treatment planning systems (TPSs) that can fully explore the myriad of solutions to the treatment problem.

However, as PBS PT has only recently become clinically mature, we have only just begun to scratch the surface of the possibilities of PBS PT, and to go deeper, many developments in the techniques and tools of treatment planning are required. Note, as robust and biological (RBE based) planning have dedicated sections in this roadmap article, in this section we will concentrate on other areas for treatment planning development that need to, or will be pursued in the coming years.

Current and future challenges

One of the major characteristics of the treatment planning of PT is its flexibility, where many solutions to the PBS planning problem provide superficially similar dose distributions to the target. As such, PBS proton treatments to the same case can vary enormously depending on the TPS used, and the inputs provided. But this flexibility is a two-edged sword. On the one side, the use of different planning practices and tools at different institutes could lead to heterogeneous and perhaps contradictory clinical results, or make patient selection, when based on comparative planning exercises, inconsistent and potentially misleading (see article on 'Selecting Patients for PT'). On the other side, this flexibility is ripe for exploitation, for instance to substantially improve the quality or deliverability of PT.

Another major issue for PT is its sensitivity to anatomical changes of the patient throughout the treatment course (Szeto *et al* 2016, Hoffmann *et al* 2017). Ideally, methods to estimate these effects should also be incorporated in the treatment planning process in order to best mitigate (see section on adaption), or record, their effects on the delivered treatment (see article on 'Adaptive Therapy'). Indeed, the issue of dose reporting, in the form of three-dimensional distributions of the estimated dose delivered to the patient, is a crucial, unique and perhaps undervalued attribute of radiotherapy and the treatment planning process. For instance, from such data, it is possible to build biological models predicting treatment outcome with ever increasing sophistication (see e.g. Wopken *et al* 2014), but models, which, in the end, can only be as predictive as the accuracy of the dose reporting itself. Thus, reporting of the actually delivered dose over the whole treatment course, rather than an estimate derived from a single calculation performed before the course commences, will become increasingly important. Finally, with the increasing investigation of new biologies with protons such as grid and FLASH irradiations (Mazal *et al* 2020), new and hitherto ignored delivery parameters, such as estimates of delivered dose rates and/or biological models estimating their effects, will need to be incorporated into the planning process (see article on 'Delivery Technology').

Advances in technology to meet challenges

Exploiting and taming flexibility. Much still needs to be done to fully exploit flexibility in PBS proton treatments. Obvious examples are developments in robust and LET based optimisation, both of which are covered in detail in other sections of this article (see also roadmap articles on 'Robust Optimization' and 'RBE Clinical Impact'). However, an as yet, not fully exploited potential is the optimization of pencil beam placement within the field. For instance, as has been shown by Meier *et al* (2017), dose confirmation can be substantially enhanced using more flexible spot placement techniques such as contour scanning, where pencil beams are first placed on exactly the surface contour at any given depth, thus contracting the high dose contour closer to that of the target volume. Alternatively, spectacular reductions in the number of pencil beams per field, whilst preserving or even improving dose conformation, have been demonstrated through the inclusion of 'spot reduction algorithms' into the optimization process (van de Water *et al* 2013). Such approaches however can be considered to be just surrogates of the true 'holy grail' of PBS planning—the ability to flexibly and comprehensively include spot placement, spot size and delivery dynamics (e.g. energy switching layer and scanning times) directly into the optimization process, and much interesting work remains to be done in this direction.

There is similar potential in the optimization of field directions and plan geometries. By plan geometries here, we mean the not necessarily trivial combination and overlapping of different fields during the planning process. For instance, one of the major advantages of the stopping characteristics of protons is the ability to significantly spare normal tissue through the use of 'split fields', whereby different fields cover different portions of the full target volume or volumes (see e.g. Lomax 1999, Widesott *et al* 2011). In the future, such approaches

will be included directly in a comprehensive optimization approach including both field directions and (if necessary) target splitting. Although it is clear that the degrees of freedom open to the optimizer for such an approach are huge, such developments will be pursued in parallel with the development of ultra-fast dose calculation engines (Matter *et al* 2019) which can efficiently and quickly search the huge solution space that is opened by such techniques. Indeed, such developments will also open the door to a more automated, and therefore consistent, approach to the treatment planning of PBS PT, a solution that will also be augmented by developments in machine learning and knowledge based approaches to the treatment planning problem. Indeed, such developments may well be decisive in 'taming' degeneracy in treatment planning of PBS PT, introducing planning consistency, thus enabling a more fair and effective method for selecting patients for PT when working with (e.g.) model based approaches (see e.g Bijman *et al* 2017). As such, the current downside of the flexibility of PBS PT—potential inconsistencies in plan quality between centers and plans—will be drastically reduced.

Mitigating anatomical change. The mitigation of anatomical changes in PT is particularly challenging for many sites, simply because the nature of those changes are difficult to predict. However, in some sites, anatomically robust optimization has been shown to be possible where such changes are localized and can be well modeled (van de Water *et al* 2018, Cubillos-Mesías *et al* 2019, Yang *et al* 2020), and more developments are foreseen in this direction (see article on 'Robust Optimization'). In particular, the use of morphological changes to the planning CT to model potential weight changes or physiological deformations (Kainz *et al* 2019) may have promise as future inputs to anatomical robust optimization approaches. On the other hand, and as described in detail in another contribution to this article (see also roadmap article on 'Adaptive Therapy' and Albertini *et al* 2020), the management of anatomical change will move more and more into the direction of rapid, even daily adaption of the treatment to 'anatomy-of-the-day' volumetric image taken immediately before the delivery of each fraction.

Such an approach poses a number of challenges, and opportunities, to the treatment planning process, such as the delineation of target and OAR's on the daily volumetric data set, ultra-fast plan adaption or re-optimization, and efficient and automated plan verification tools. For target and OAR definition on the daily image set, either accurate and reliable deformable warping of the original volumes between the original plan and the daily patient geometry, or fully automatic delineation algorithms will need to be developed. Indeed, many advances have been made recently in the latter (Giraud *et al* 2019), and it would seem that this is the direction with the most promise in the future. Even with this approach however, additional developments in TPSs will need to be made in order to provide the clinician with feedback on the 'plausibility' of the automatically generated or deformed contours before applying the adapted plan, and such tools must be efficient enough to not substantially delay the adaptive process.

Rapid plan adaption, such that a completely new or adapted plan can be calculated and validated in just a few minutes, will require developments in ultra-fast dose calculations and optimization, or alternatively, methods to determine and correct just those pencil beams of the original plan most affected by the changes (Botas *et al* 2018). Indeed, for adaptive plan optimization, different approaches can be foreseen. First, dose-restoration techniques may be used, whereby the plan-of-the-day is automatically adjusted to be as close to the original plan as possible, substantially mitigating the amount of plan specific validation and verification necessary (Bernatowicz *et al* 2018). Alternatively, tools for a full, 'from scratch' re-optimization, potentially involving beam angle adjustments as well, will be developed, which can additionally take into account any preferential features of the anatomy of the day, helping to possibly improve the quality of the treatment in relation to the original plan (Nenoff *et al* 2019). Similarly, and as proposed by Yan in his seminal paper on adapted therapy (Yan *et al* 1997a, 1997b) feedback loops could be incorporated into the adaptive process, whereby the accumulated doses from previous fractions are used as an input to the daily optimization process. This way, the 'plan-of-the-day' could also adapt on any deviations of the accumulated dose away from the reference plan (for instance as a result of interrupted previous treatments) or even capitalize on advantageous anatomical changes taking place over the course of the treatment (see e.g. Matter *et al* 2020).

Finally, alternative, treatment planning based methods for plan validation will need to be developed, such as fast, fully independent dose calculations which can reconstruct the dose from (e.g.) machine control data before the plan-of-the-day is delivered (Matter *et al* 2019). Such developments will require an ever closer cooperation between the delivery machine and TPS manufacturers (see article on '4D planning and Delivery').

Clinically relevant dose reporting. As we move towards treatment adaption to multiple imaging data sets of the patient, the problem of recording what dose was actually delivered to the patient at what point becomes increasingly challenging. However, such data is essential for the development of accurate biological models for outcome prediction (see article on 'Outcome Modeling'). Although tools for registering two or more data sets together in 3 dimensions are mature, particularly for the deformable problem, the solution is notoriously

degenerate, with different systems providing quite different solutions (Nie *et al* 2016, Nenoff *et al* 2020). As such, future developments in dose accumulation, together with associated 'uncertainty' maps indicating those regions where the accumulated dose can be trusted to a greater or lesser extent, will need to be developed (Heinrich *et al* 2016). This would be analogous to the calculation and presentation of dose uncertainty as part of robust plan analysis methods already available in most commercial TPSs. Indeed, uncertainties of all types are an integral part of the radio- and PT process, and as such can provide valuable information to the planning physician or also, eventually, as an additional parameter to include into outcome analysis and biological modeling. As such, dose reporting should also include standardized ways of reporting spatially varying uncertainties in calculated and delivered dose, as well as biological parameters such as LET, both of which are important for PT if we wish eventually to understand their clinical relevance.

Planning for new biologies. Finally, it is perhaps too early to speculate on what changes to TPSs will be required to plan for FLASH or Grid irradiations. For both, current dose calculation engines will likely be accurate enough to provide accurate estimates of the three-dimensionally varying dose delivered to the patient. But given that the response of tissue to both techniques will be quite different to that of conventional therapy, even before we develop the appropriate biological models, new metrics for quantifying such plans will need to be developed. For FLASH, this will likely be in the direction of spatially varying spectrums of dose-rates (van de Water *et al* 2019, van Marlen *et al* 2020) which would, similarly to the validation of adaptive plans discussed above, require a close cooperation between treatment machine and therapy planning manufacturers. Based on these, and as our knowledge of the clinical FLASH effect becomes deeper, there will be the need to start to incorporate a biological 'FLASH' effect as a function of dose rate, in an analogous way to RBE and its relationship with LET. Only through the development of such tools can we hope to be able to effectively plan FLASH treatments. For grid-based treatments, other tools may be necessary. As the sparing of normal tissue will be dependent on the peak-to-valley dose ratio and its spatial separation, TPSs may need to provide tools for quantifying and optimizing this in an analogous way to dose volume histograms, or provide metrics for quantifying the heterogeneity (or 'gridness') of the dose distribution in normal tissues and the tumor.

Concluding remarks

The relative immaturity of PBS PT, together with the need to mitigate (and record) uncertainty, leads naturally to many challenging and interesting developments still to be done in the treatment planning of PT. When also considering the exciting areas of FLASH and grid therapy, which are themselves challenging our conventional thinking of biology and what is a 'good' treatment plan, developments in treatment planning are anything but dead. Indeed, it is an area ripe to be exploited and where much still needs to be done.

8. Development of robust planning

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PT practitioners have long been aware of dose uncertainties in PT and have developed strategies to account for uncertainty in treatment planning (Paganetti 2011) (see article on 'Uncertainties'). In the era of passive scattering based PT, this included increasing range and modulation of spread-out Bragg peaks, widening apertures, and compensator smearing. For complex geometries requiring patch fields, multiple patch field combinations were used to mitigate the effect of misaligned fields. In the era of pencil beam scanning, treatment planning became based on mathematical optimization techniques similar to intensity-modulated radiotherapy (IMRT). The similarity to IMRT made it natural to apply the PTV concept to PT planning. However, it was soon realized that the PTV concept has limitations in PT. The fundamental assumption behind the PTV concept, that the CTV receives the prescribed dose as long as it moves within the PTV, is not generally valid for PT. Range and setup errors may lead to misalignment of dose contributions of different beams, misalignment of tissue heterogeneities in the entrance region may degrade dose distributions, and thus PTV coverage does not guarantee CTV coverage even if PTV margins are large. A commonly used heuristic to improve robustness is referred to as single field uniform dose (SFUD), which mitigates dose degradation due to misalignment of dose contributions from different beams. However, for complex shaped target volumes, SFUD compromises treatment plan quality compared to IMPT. In addition, dose degradation due to misalignment of tissue heterogeneities is not addressed. Robust optimization methods were developed to address these limitations and refer to mathematical optimization techniques that directly incorporate uncertainty into the formulation of the IMPT optimization problem.

Status of robust optimization

Robust planning can be divided into robustness evaluation (i.e. assessing the sensitivity of a given treatment plan to errors) and robust optimization (i.e. the process of obtaining a treatment plan that is robust against errors). In photon therapy, robustness is indirectly assessed by evaluating the dose distribution in the PTV. As it has been recognized that coverage of the PTV does not guarantee coverage of the CTV in PT, the main commercial TPS now allow for evaluating the dose distribution for individual error scenarios. In addition, various measures to assess dose uncertainty such as confidence intervals around DVH lines have been suggested but only a subset of those is available for practitioners. In addition, the main TPS have an implementation of robust optimization. (see article on 'Treatment Planning').

In IMPT optimization, an objective function f, which is a function of the dose distribution d, is minimized with respect to pencil beam intensities x. Under uncertainty, given pencil beam intensities x may lead to different dose distributions d_s for error scenario s. Practically, the goal is to obtain a treatment plan that is of high quality for all or most anticipated errors. There have been three approaches to translate this practical goal into mathematical terms that led to implementations in the main commercial TPS.

1. Stochastic optimization, also referred to as probabilistic treatment planning, assigns probabilities p_s to the error scenarios and optimizes the expected plan quality (Unkelbach *et al* 2009). This approach is implemented in the Pinnacle planning system (Philips Healthcare).

$$\underset{x}{\text{minimize}} \sum_s p_s f(d_s(x))$$

2. Minimax optimization (Fredriksson *et al* 2011), also referred to as composed worst case optimization, determines the pencil beam intensities such that the dose distribution is as good as possible for the worst error scenario considered. Minimax optimization is implemented in Raystation (Raysearch Laboratories).

$$\underset{x}{\text{minimize}} \left[\max_s f(d_s(x)) \right]$$

3. Optimization of the voxel-wise worst case dose distribution (Pflugfelder *et al* 2008) can be considered a variation of minimax optimization. Here, the minimum doses in target voxels and the maximum doses in normal tissue voxels are considered. The resulting voxel-wise worst-case dose distribution is used for evaluating the objective function. The approach is implemented in Eclipse (Varian).

Other methods, such as minimax stochastic optimization (Fredriksson 2012), which interpolates between optimizing average and worst-case plan quality, have been proposed, but are currently not available for practical use in commercial systems. An extensive review is provided elsewhere (Unkelbach *et al* 2018). For illustrations of

robust optimization and comparisons to PTV-based plans, we refer to the original publications. The variety of methods implemented in different commercial systems suggests that there is no single robust planning method that is found to be generally superior. It has been shown that individual methods have disadvantages in specific situations, however, in most cases different robust planning yield very similar results. Publications comparing methods are scarce. Regarding the types of uncertainty, most of robust IMPT planning research has focused on systematic range and setup errors. In the research literature, extensions to other uncertainties such as respiratory motion have been considered but are only partially supported in some TPS. (See articles on 'Treatment Planning' and '4D Planning and Delivery'.)

Current limitations and future challenges

Establishing consensus for robustness evaluation. In photon therapy, plan robustness is indirectly assessed by evaluating coverage of the PTV. Although this may have limitations also in photon therapy, it allows for establishing consensus that is needed, for example, in the design and reporting of multi-institutional trials. Concepts for robustness evaluation for protons have been proposed (Korevaar *et al* 2019). However, there is no general consensus yet on how to assess and report the robustness of proton plans, which should be addressed in future working groups.

Optimization based on relevant plan quality indicators. Most robust optimization methods currently available were developed by applying known methods from the optimization literature such as minimax or stochastic optimization to the IMPT planning problem. Thereby, common objective functions such as quadratic penalty functions are robustified. However, the expectation or worst-case values of quadratic penalty functions are only surrogates for plan quality. In practice, DVH based criteria are considered, for example, a treatment plan may be acceptable if 95% of the target volume receives the prescription dose in 90% of the scenarios. Future work may aim at facilitating robust treatment plan optimization using relevant plan quality indicators as objective and constraint functions.

Beyond systematic range and setup errors. Current research and support in commercial systems has focused on systematic range and setup errors. Typically range errors are modeled by up- or down-scaling of Hounsfield units of the planning CT. Thereby, it is assumed that range errors affect all pencil beams in the same way, that is, all pencil beams overshoot or undershoot synchronously. Setup errors are modeled as rigid shifts of the patient. These models of uncertainty are simple to implement, however, the real source of uncertainty is more complex. Today, range and setup errors are used as surrogates for other uncertainties such as internal organ motion (see articles on 'Adaptive Therapy' and '4D Planning and Delivery'). Complex geometric variation is difficult to model based on a single planning CT scan prior to treatment. Nevertheless, future work may consider the development of site-specific uncertainty models for evaluation and optimization that reflect the characteristic uncertainty of specific treatment sites (see article on 'Treatment Planning').

Computationally efficient methods. Robust optimization remains a computationally demanding task, depending on the number of scenarios considered, and may lead to long computation times. Several approaches to address computation time are being investigated and may be brought to an application in the future. Perko *et al* (2016) developed a methodology allowing fast robustness evaluation of treatment plans. In their approach, the dose distribution is evaluated for a limited number of error scenarios; subsequently, these dose distributions are fit with a set of polynomial basis functions. Thereby, a model of the dose distribution as a continuous function of the error is obtained, which can be used for further robustness evaluation at almost no additional computation time. Bangert *et al* (2013) pursue an alternative approach to probabilistic treatment plan evaluation and optimization going beyond a discrete set of error scenarios. The underlying idea is to consider Gaussian range and setup errors in combination with a Gaussian parameterization of pencil beam dose distributions. In that situation, one can exploit the fact that the convolution of Gaussian functions can be done analytically. This allows, for example, efficient evaluation of the expectation and variance of the dose distribution.

Applications to biological uncertainties. So far, robust optimization was mostly investigated for geometrical uncertainty. In parallel, treatment planning methods to account for variable RBE have been researched. This includes treatment plan optimization based on RBE-weighted dose (Wilkens and Oelfke 2005), but also methods to incorporate linear energy transfer (LET) into IMPT optimization (see article on 'RBE') . One of the challenges in this domain is the uncertainty in RBE. Some LET-based methods can be understood as heuristics to make IMPT plans robust against uncertainties in RBE. However, an alternative is to apply robust optimization techniques to account for uncertainty in the parameters of an RBE model (Unkelbach and Paganetti 2018). This

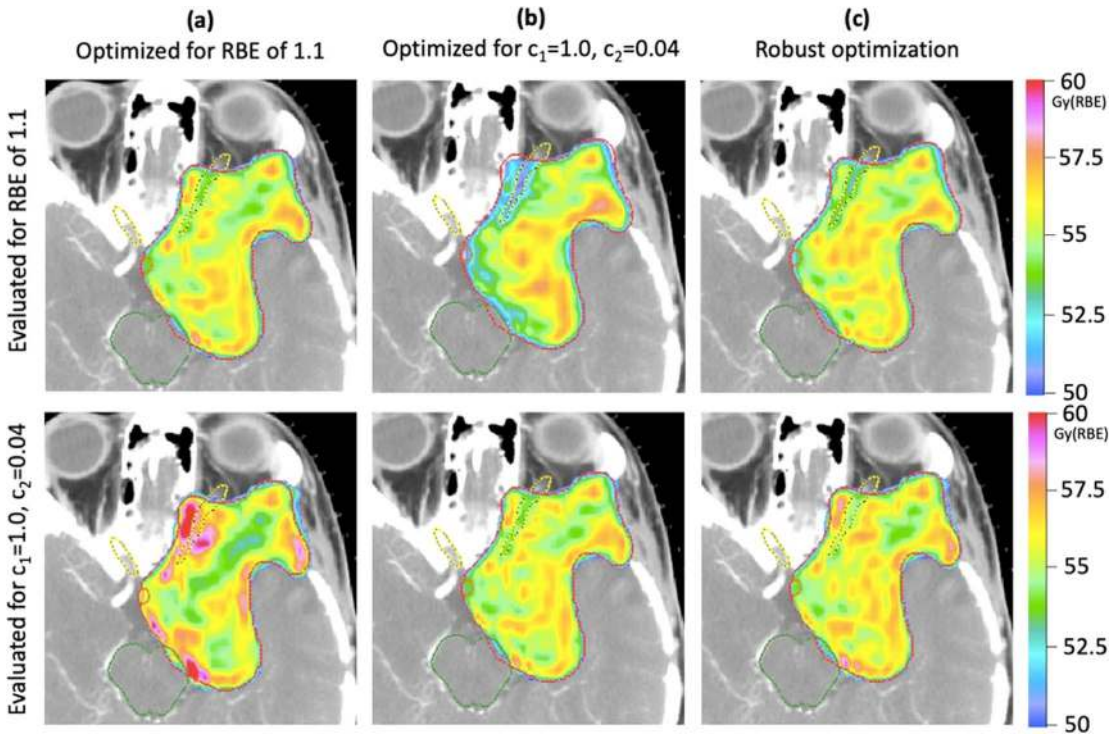

Figure 1. Illustration of stochastic programming applied to parameter uncertainty in RBE models. A simple model for RBE-weighted dose, RBE $\cdot\, d = (c_1 + c_2\ \text{LET}) \cdot d$, is considered. RBE uncertainty is modeled via 3 scenarios: (1) a constant RBE of 1.1 ($c_1^s = 1.1,\ c_2^s = 0$), (2) a variable RBE with ($c_1^s = 1.0,\ c_2^s = 0.04\ \mu\text{m keV}^{-1}$). This corresponds to the assumption that the RBE of a proton pencil beam is 1.0–1.1 in the entrance region, 1.2–1.3 near the Bragg peak, and 1.5–1.6 in the falloff region. (3) an intermediate scenario ($c_1^s = 1.05,\ c_2^s = 0.02\ \mu\text{m keV}^{-1}$). An RBE-weighted dose of 54 Gy(RBE) is prescribed to the target volume, and 57 Gy(RBE) was allowed in parts not overlapping OARs. (a) (Bottom row) demonstrates the problems with conventional planning based on a RBE of 1.1. When evaluated for variable RBE, hot spots >60 Gy(RBE) in OARs overlaying the target can be observed, resulting from high LET. (b) (Top row) shows issues with IMPT optimization based on a fixed RBE model. The method leads to lower physical doses in parts of the target, potentially leading to underdosage (<50 Gy(RBE)) if the LET effect on RBE is overestimated by the model. (c) Shows that robust optimization incorporating RBE uncertainty yields adequate target dose distributions in both situations.

is illustrated in figure 1 for an atypical meningioma patient in whom the target volume (red) overlays the brainstem (green) and the optic nerves (yellow).

Concluding remarks

Robust planning support is implemented in the main commercial TPS for PT. Thereby, robust optimization has matured from a research topic to a technique that is routinely used for treatment planning in clinical practice. Future work in this domain may aim at establishing consensus for robustness evaluation and reporting, facilitate robust optimization based on such agreed-upon robust plan quality indicators, develop site specific uncertainty models beyond systematic range and setup errors, and reduce computation times for robust planning.

9. Adaptive therapy to account for daily anatomy and range variations

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Status

It is well recognized that the PT dose distributions are more sensitive to patient's anatomic changes (Engelsman *et al* 2013, Muller *et al* 2015, Hoffmann *et al* 2017) (see article on 'Uncertainties') compared to photon therapy. Adaptive radiation therapy (ART) is becoming a critical tool for some treatment sites, such as head and neck (Gora *et al* 2015, Muller *et al* 2015) and lung cancers (Hoffmann *et al* 2017) which are known to have large anatomical changes during treatment course due to treatment effects, such as tumor shrinkage, weight loss, pleural effusion, atelectasis etc. It is a common practice to repeat the simulation CT to evaluate patient's anatomical changes and re-calculate the original proton plan on the updated CT or 4DCT images to assess target coverage and normal tissue sparing. When necessary, offline ART is performed to improve dose conformality.

Unlike photon therapy, there are additional factors that can trigger a proton plan adaptation. For example, changes outside of the target volume, which include but are not limited to radiological pathlength variations due to patient's anatomy, changes of couch top or immobilization devices relative to the simulation position, heterogeneity changes etc. While robustness optimization is a planning strategy to manage potential rigid setup errors and expected range variations, ART is a personalized approach to deal with actual changes during treatment.

Although offline ART is becoming a common practice in PT, it is still a time- and resource-consuming process. The primary steps in ART include re-simulation, re-contouring, original plan evaluation, and re-plan (ART) if necessary, with the associated QA procedures for new plans. While some of these steps can be assisted by auto-segmentation or auto-planning tools, human intervention is still required because these tools are not perfect and there are many required steps (such as manual importing images, physician's availability and adequate time to review plans etc), even if computational resources are not a constraint. There are no clear guidelines on how often patients should be evaluated for anatomical changes or well-defined criteria that should be used to trigger ART. Nevertheless, in-room volumetric imaging using CBCT or CT-on-rails has become a standard configuration for modern PT (Landry and Hua 2018); qualitative or quantitative evaluations of patient's anatomy have become more convenient. This trend of using online volumetric imaging should increase the utilization of ART for PT in the near future.

Current and future challenges

ART is an interventional process that requires adequate feedback (online/offline imaging), decision support (criteria for replanning) and corrective strategies. The general process and selected contents specific to PT are summarized in figure 2. It is important to realize that there are many factors that can impact conformal dose delivery. Proton ART may be limited by the correction strategies (offline, online or real-time) or imaging techniques to detect specific changes in patients. An offline ART approach can correct systematic or slow changes in anatomy, but may be limited in adapting daily physiological variations in setup position.

Although the offline ART seems to be a practical approach, the process itself can benefit from streamlining and automation in many steps: CT image artifact removal, density overrides for couch/immobilization structures, auto-contouring of targets and OARs, faster dose calculation and plan comparison tools. If a new ART plan is requested, a faster treatment optimization and efficient QA may be needed. Sometimes, transferring the approved plan to vendor's treatment console and updating treatment calendar for the new plan would require additional manual intervention. Because this is a time-consuming manual process, few PT patients are currently benefiting enough from offline ART. For those centers that do, imaging frequency, contouring, and quality of ART plan may be suboptimal due to time constraint and resource limitations. Therefore, the current biggest needs are the development of automation tools that can support proton ART workflow.

Recently, there has been enormous progress in developing online adaptive photon therapy (Wang *et al* 2017). Some of these tasks are identical for proton ART (for example, auto-segmentation on CT or CBCT images) while others share a similar approach. For example, the use of GPU for fast dose calculation or plan optimization (Matter *et al* 2019), and QA (Wang *et al* 2017), which are critical for online ART. Near real-time dose restoration to account for daily tissue density variations using an on-line range adaptation of individual spot energies (Zhang *et al* 2011) with readjustment of some spot weights (Jagt *et al* 2017) is one approach that permit fast plan re-generation for online ART (see section on Treatment planning for pencil beam scanning PT). A summary of proton ART strategies and correction goals are listed in figure 3.

A more difficult problem is to convert Hounsfield Unit (HU) from online CBCT images into accurate proton stopping power ratios that are required for dose calculation. Some investigators used a virtual CT approach,

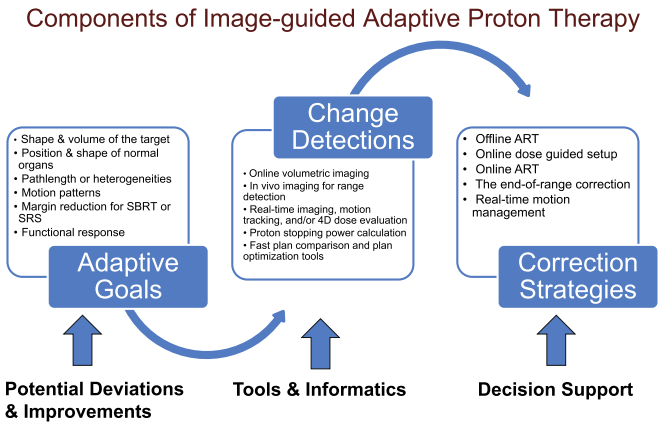

Figure 2. Adaptive proton therapy is an interventional process that requires imaging and algorithms to detect changes and identify improvements, and then a subsequent corrective strategy.

Variation Factors	Offline ART	Online ART	Online Range Adapted RT
Systematic WET/Target	✓	✓	✓
Daily WET/Target	X	✓	✓
Proton Range Calculation	X	X	✓
Distal OAR Sparing	X	?	✓
Intra-fractional Motion	X	?	?

Figure 3. Scoring sheet for common online/offline correction strategies and their corresponding uncertainties. WET: water-equivalent-thickness; OAR: organ-at-risk.

which matches CBCT HU to the corresponding simulation CT images using a deformable image registration method (Veiga *et al* 2016) and others used scatter correction to create a high quality CBCT similar to the conventional CT scanner (Nomura *et al* 2019). Recently, machine learning based approaches seem promising in directly converting CT numbers (CTNs) into proton stopping power (Kurz *et al* 2019, Nomura *et al* 2019). Each of these approaches creates additional uncertainties, which should be factored in the implementation of ART.

An ideal approach for online ART might involve the use of *in vivo* imaging for proton range correction (see article on '*In vivo* range verification'). Because range uncertainties are the primary reason for plan adaptation and also responsible for suboptimal quality in the original plan due to uncertainties in proton stopping power conversion (Yang *et al* 2012), an online range-adapted PT approach would be appealing if the proton range can be accurately detected and corrected just prior to treatment delivery. *In vivo* range detection is still under intense research, and investigated approaches include but are not limited to (1) in-room proton CT (Sadrozinski *et al* 2016); (2) prompt gamma detection (Xie *et al* 2017, Hueso-Gonzalez *et al* 2018); (3) proton radiography (Deffet *et al* 2017); (4) proton-acoustic wave detection (Patch *et al* 2019) etc. If successful, one additional benefit is to use the sharp falloff of the Bragg peak to spare distal OAR, which has not been fully utilized in conventional PT due to range uncertainties (Hoesl *et al* 2016). Data from *in vivo* imaging can be used in two ways. First, if systematic range shifts due to inaccuracies in proton stopping power are detected, the plan may be adapted to reduce these shifts for subsequent fractions. Second, *in vivo* range verification offers a real-time QA of the online ART plan when traditional measurement-based QA with phantom is not feasible.

Other challenges are related to the rapid variation of proton range due to breathing motion and beam interplay effects (Mori *et al* 2018). For treatment sites that experience a large organ motion, 4D cumulative dose calculation may be needed to evaluate plan robustness for both inter- and intra-fractional changes (Li *et al* 2012) (see article on '4D planning and delivery'). ART planning may need to incorporate plan robustness to minimize motion effects (Liu *et al* 2016). ART planning can also be used to compensate patient specific motion patterns (Li *et al* 2015).

Concluding remarks

Due to many technical and practical issues, proton ART is in its infancy. The biggest challenge now is to develop reliable tools (such as data processing, informatics, plan review, decision support, auto-planning, QA etc) to

make the entire process more efficient and practical. Currently, there is no consensus on what anatomic or dosimetric change would be required to trigger ART that will optimize the treatment. However, the dosimetric benefit of proton ART is well accepted by the PT community. Parallel to the development in photon therapy, online proton ART is the upcoming strategy that can bring perhaps the biggest dosimetric benefit to PT patients (Albertini *et al* 2020). Ultimately, the success of ART has to be associated with improved clinical outcome. Although this was just one isolated study, Yang et al demonstrated that ART made 5-year overall survival for a subgroup of lung cancer patients with large tumors (poor prognostic condition) similar to that of small tumors, presumably due to improved dose conformality (Yang *et al* 2019). More studies are needed to confirm such findings.

10. *In vivo* range verification

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Status

Already back in the early pioneering phase of PT, Bennett *et al* postulated the possibility of controlling the surface of maximum beam penetration, which relates to the ability of depositing the dose maximum (Bragg peak) in the tumor while sparing the normal tissue behind, by visualizing the β^+-activity generated through nuclear interactions of protons in tissue (Bennett *et al* 1978). Their seminal work not only showed that a prototype on-line positron emission planar camera was able to visualize in a live pig the pattern of proton-induced activation, which was mostly ascribed to ^{11}C, ^{15}O and ^{13}N fragmented tissue nuclei, but also foresaw the use of such positron emission measurements for reconstruction of the delivered dose. Moreover, they emphasized the importance of on-line detection for analysis of the biological transport of irradiation-induced radionuclides, which is relevant to the localization and reconstruction of the delivered dose, and even suggested to provide useful information on regional blood flow. Nevertheless, due to the technological challenges for development and integration of dedicated positron-emission-tomography (PET) scanners in the treatment delivery, most of the following investigations in phantoms and first clinical pilot studies were pursued after treatment using nuclear medicine PET and PET/computed tomography (CT) full-ring diagnostic scanners (Parodi and Polf 2018). Such in-room and offline volumetric imaging approaches suffer from issues of physical and biological decay in the time elapsed between irradiation and imaging, along with possible changes of the patient position, all degrading the correspondence between the physically produced and the image reconstructed activity (Shakirin *et al* 2011, Parodi and Polf 2018). Although most of these issues can be overcome with the ongoing re-implementation of on-line detection approaches (Shakirin *et al* 2011, Ferrero *et al* 2018, Parodi and Polf 2018), the PET signal can be considered intrinsically delayed with respect to the beam delivery according to the half-life of ~2–20 min of the most abundant positron emitting reaction products. Hence, in 2003 Stichelbaut and Jongen raised the question why not verifying the proton beam position in the patient by the detection of prompt gamma (PG) rays emitted in the very fast (sub-ns scale) de-excitation processes after nuclear interaction (Krimmer *et al* 2018). However, due to the high energies of such PG emissions in the MeV range, it took several years of computational simulations and detector development (Krimmer *et al* 2018) to arrive at first viable prototypes of collimated cameras (Xie *et al* 2017, Hueso-Gonzalez *et al* 2018), only able to capture a one- or two-dimensional projection of the distal PG signal generated from each individual pencil beam delivered to the patient. Remaining challenges entail further improvements of detector technologies along with interpretation and utilization of these (or even other) secondary emissions, typically in comparison to an expectation, to devise new strategies for ideally real-time beam range verification and quantification of the actual dose delivery for prompt treatment adaptation. These efforts will also largely benefit from as well as complement the ongoing developments in in-room volumetric and even time-resolved anatomical IG (see article on 'IG').

Current and future challenges

State-of-the-art on-line PET and PG detectors are just entering the phase of clinical evaluation with the most modern form of scanned proton beam delivery. At the combined proton and carbon ion therapy facility of CNAO (Centro Nazionale di Terapia Oncologica) in Italy, a dual-head PET scanner based on modern scintillation crystals (Lutetium fine silicate) and photosensors (multi-pixel photon counters) is used to dynamically (every ≈10 s) reconstruct the irradiation induced activity during treatment, with very promising initial clinical results (figure 4) (Ferrero *et al* 2018). Here, a major challenge is the still outstanding ability of using the events measured during the actual beam delivery (spills), due to remaining background from prompt radiation (including PG), despite a dedicated data acquisition system aiming to suppress it. Moreover, reconstruction and visualization of the data acquired during the interrupts (pauses) of the synchrotron-based beam delivery still requires 6 seconds, impeding a truly real-time imaging. It seems possible to achieve sub-mm reproducibility of distal range measurements in different treatment days, but accuracy between PET measurements and predictions remains at the still unsatisfactory level of a few millimeters (figure 4) (Fiorina *et al* 2018), thus demanding further improvements of the underlying modeling. The ongoing clinical evaluation and further methodological improvements will thus enable assessing whether the desired range localization accuracy of less than 1–2 mm can be achieved, going beyond the reported accuracy of PET-based verification in the order of 2–5 mm for the earlier less optimal clinical implementations (Parodi and Polf 2018, Parodi 2018).

For PG, two prototypes of a single slit camera, consisting of a knife-edge collimator and position sensitive Lutetium-yttrium oxyothosilicate scintillators readout by silicon photomultipliers (Xie *et al* 2017,

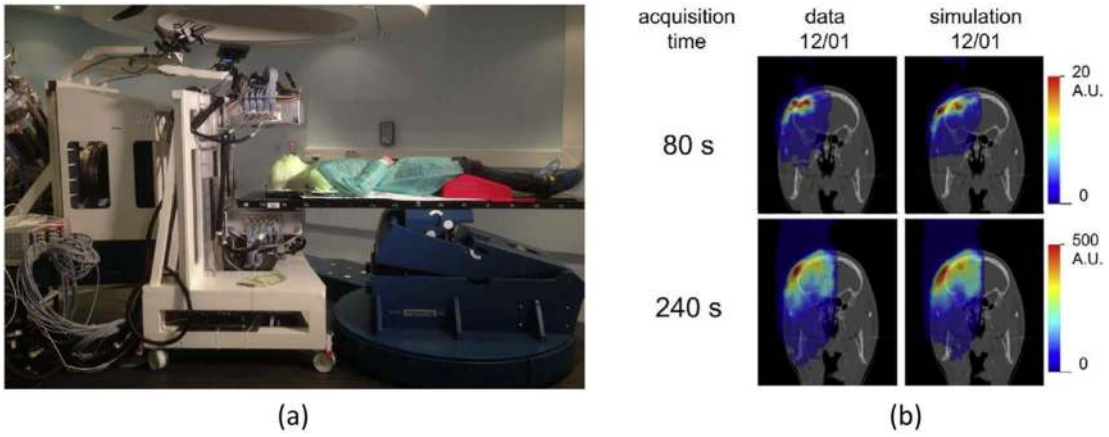

Figure 4. Example of the dedicated in-beam PET scanner in treatment position at CNAO (a) and the dynamically reconstructed PET activation data in comparison to the simulated predictions (b) in two different time windows during proton beam delivery. The PET images (color wash) are superimposed onto the planning x-ray CT (gray scale). Adapted from Fiorina *et al* (2018), Copyright © 2018 Associazione Italiana di Fisica Medica. Published by Elsevier Ltd. All rights reserved.

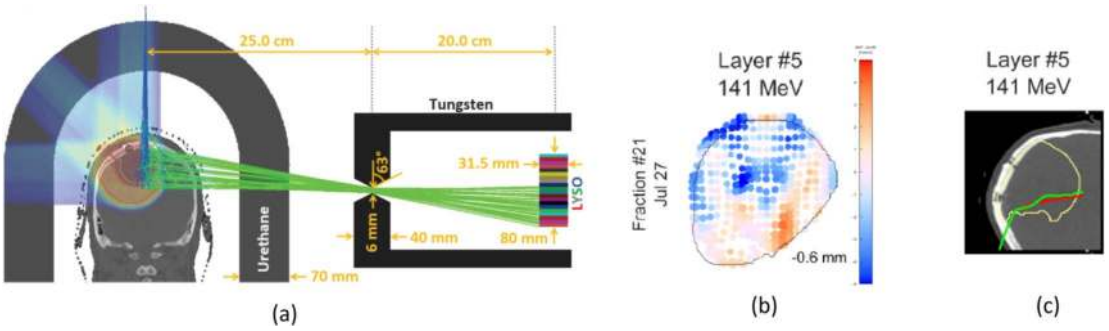

Figure 5. (a) Schematic of the knife-edge slit camera, as deployed in the first clinical study of (Xie *et al* 2017), projecting the PG signal (green) from the proton beam (blue) onto the position sensitive scintillators beyond the collimator. The corresponding analysis results in the spot-by-spot (with aggregation) range difference comparison in beam-eye-view (b) as well as PG-based estimation of the measured (green) and predicted (red) Bragg peak depth overlaid with the planning CT (c) for a given energy layer and treatment fraction. Adapted from Xie *et al* (2017), Copyright © 2017 Elsevier Inc. All rights reserved.

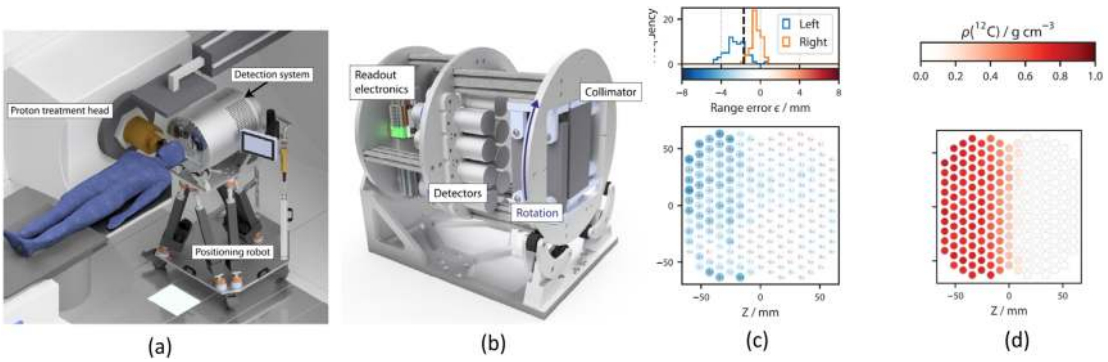

Figure 6. Schematic of the spectroscopic system of Hueso-Gonzalez *et al* (2018) integrated in the proton beam gantry for a representative treatment position (a), along with the details of the energy- and time-resolved detector components beyond the collimator (b). The results enable quantifying the range difference from a prediction model for each applied spot (c) along with carbon (d) and oxygen concentrations, in this example obtained when inserting a slab phantom on the left of the beam path in water (with spot aggregation). Adapted from Hueso-Gonzalez *et al* (2018). © 2018 Institute of Physics and Engineering in Medicine. All rights reserved.

Krimmer *et al* 2018), are being investigated for their ability of spot-by-spot proton range recovery at University of Pennsylvania (figure 5) and University PT Dresden. The initial clinical evaluation showed the feasibility of achieving precision (defined as standard deviation of random simulated shifts) within 2 mm when aggregating the signal from nearby pencil beams for sufficient ($\geqslant 1.2 \times 10^8$ protons) counting statistics. However, the clinical

findings of average (aggregated over all spots in 9 energy layers) range shifts from −0.8 to 1.7 mm between measurement and expectation were mostly limited by the mechanical accuracy of the trolley positioning system, for which improvements are currently ongoing. Still, the design of this detection system can only provide one-dimensional profiles of coarse spatial resolution, challenging the performance in the presence of considerable tissue heterogeneities that distort the distal dose surface, or large tumor sizes that require a wide dynamic range of the camera field-of-view coverage. More recently, another collimated system featuring eight $LaBr_3$ scintillators behind a tungsten collimator, mounted on a rotating frame, has been thoroughly characterized experimentally prior to its clinical deployment (figure 6) (Hueso-Gonzalez *et al* 2018). The detection system has been optimized for energy and time resolution to enable spectroscopic analysis of the gamma emissions characteristics of each specific tissue nuclei and for optimal suppression of radiation background outside the microscopically bunched beam extraction from the cyclotron. By comparing the measured signal with a sophisticated prediction model taking into account experimental data of PG emissions for different nuclear reaction channels as well as possible range error scenarios, the system can provide spot-by-spot maps of range difference (between measurement and prediction) and percentage elemental composition of carbon and oxygen (figure 6). Investigations in phantoms suggested the feasibility to retrieve the proton beam range with a mean statistical precision of 1.1 mm at a 95% confidence level and a mean systematic deviation of 0.5 mm (Hueso-Gonzalez *et al* 2018). Hence, this level of accuracy, if confirmed in the ongoing first clinical evaluation, would be well below the one so far reported for PET-based range verification. However, also this system requires aggregation of neighboring spots to increase the signal statistics, thus challenging the achievable spatial resolution and range resolving power in the presence of pronounced tissue heterogeneities. Moreover, none of these on-line PET and PG systems integrates imaging modalities able to provide complementary information on the tissue anatomy, for co-registration with the retrieved information of the distal beam penetration depth as well as updated patient model for attenuation (and scatter) correction.

Advances in science and technology to meet challenges

Ongoing research in the medical imaging community towards detectors of ultra-fast timing resolution in the order of 10 ps, along with steady progress in real-time data acquisition and processing, will certainly benefit the above described detector designs, ideally enabling real-time imaging as well as improved background suppression and image quality (Lecoq *et al* 2020). For PET-based range verification, additional efforts are ongoing to exploit the signal from millisecond short-lived positron emitters (e.g. ^{12}N) to enable quasi real-time visualization of the dynamic beam delivery (Buitenhuis *et al* 2017), although likely at the expense of degraded spatial resolution from the typically long positron range. For PG imaging, efforts are ongoing to increase the dimensionality of the reconstructed distribution and to remove the massive collimator for enhanced detection efficiency. To this end, several prototype designs of Compton cameras have been proposed based on different detector technologies (solid state, scintillation, and thereof combination), along with alternative approaches exploiting only the arrival time of the photons or their conversion into secondary electrons (Krimmer *et al* 2018). Exploitation of the Compton kinematics also opens the perspective of new unconventional designs of hybrid detection systems able to reconstruct signals related to standard PET and PG emissions, as well as triple coincidences originating from special isotopes (e.g. ^{10}C, ^{14}O) that emit an additional third photon in connection with their radioactive decay (Lang *et al* 2014). Besides utilization of complementary photon emissions (e.g. PG during beam-on and PET during beam delivery pauses or after irradiation), triple gamma imaging offers the intriguing potential of visualizing the underlying activity with only a few detected events, thereby also opening the perspective of an almost real-time imaging, at the expense of the lower probability of such events (Lang *et al* 2014). This ability could also be exploited to combine *in vivo* range verification with additional nuclear tracer imaging for localization of the tumor or specific biomarkers to provide image-guidance during treatment, ideally also time-resolved for moving targets. Regardless of the final technological implementation and imaging approach, information on the *in vivo* range will likely still rely on a comparison between the measured and predicted signal. To this end, considerable progress is expected from the emerging ability of embedding fast predictions of PET and PG signals in treatment planning engines (Pinto *et al* 2020), which also enables accounting for the counting statistics required for reliable monitoring in the treatment planning approach (Tian *et al* 2018, 2020). Improved accuracy of these computational models will also largely benefit from the ongoing efforts of the scientific community to provide more accurate experimental measurements of underlying nuclear cross section data and resulting PET and PG yields in clinically relevant targets (Horst *et al* 2019). Moreover, advances in artificial intelligence (AI) and deep learning approaches will also support the implementation of novel and fast workflows which can provide almost real-time feedback on the dose delivery (Liu and Huang 2020) to devise prompt correction strategies even during patient irradiation.

Concluding remarks

The considerable ongoing progress in instrumentation and computational methods for PET and PG imaging will likely enable reliable and almost real-time (sub)millimeter accurate monitoring of the beam range in the patient in the near future, which would be a major step forward with respect to the so far attempted applications of these technologies in clinical pilot studies. Although PG can offer advantages in terms of range localization accuracy and real-time information, PET provides an intrinsically 3D imaging modality lending itself to the possible combination with tracer imaging. Imaging annihilation and single photon emissions with a single device (Yoshida *et al* 2020) will open new prospects for making the most of both technologies during different portions of the irradiation (e.g. PG during beam-on and PET during beam-off) and evaluate their strengths and limitations in different anatomical sites. These nuclear-based technologies of general applicability, already finding their way into clinical translation, will likely be complemented by the less mature technologies currently under investigation for specific anatomical locations, using different kinds of secondary emissions (e.g. thermoacoustics for pulsed beams or secondary protons) or pre-treatment range probes (Parodi and Polf 2018). All these efforts in range verification will also benefit from and complement the ongoing developments for improvement of the daily patient model at the treatment place based on different flavors of x-ray, proton and magnetic resonance and, especially in the case of thermoacoustics, ideally intrinsically co-registered ultrasound imaging (see articles on 'Image-guidance' and 'Adaptive therapy' as well as Parodi 2018). Together with the further development of very promising methods of dose reconstruction from the measured emissions (Masuda *et al* 2019), advances in the monitoring of proton treatment will provide real-time information of the beam position in the patient and ideally of the applied pencil-beam dose in the underlying updated patient anatomy, for prompt interruption of erroneous delivery or new adaptive treatment schemes. Also, changes in the detected signals over the course of fractionated therapy could be exploited to monitor processes correlated to treatment response, such as biological washout (e.g. accessible with PET imaging, as already shown in the seminal work of Bennett *et al* 1978) or oxygen concentration (e.g. accessible with PG spectroscopy) (Parodi and Polf 2018), as recently reported for phantom studies by (Martins *et al* 2020). This would thus open a new dimension of biology-driven treatment personalization, beyond the more physics-driven scope of range monitoring and dose reconstruction for truly adaptive therapy.

11. 4D planning and delivery

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Status

By now the great majority of new PT centers is equipped with pencil beam scanning (PBS) solely. The high precision of PBS-PT comes as a double-edged sword, especially for moving targets. Highly conformal dose distributions have to be delivered in a robust manner to address the high sensitivity of PBS-PT to uncertainties. Over the past few years, treatments for lesions with intra-fraction motion significantly increased in number due to the availability of robust optimization, evaluation and QA tools, increasing confidence. However, the influence of uncertainties has to be further minimized to exploit the full benefit of PBS-PT for moving indications of all characteristics.

Current and future challenges

4D imaging. Inter-fractional variations of breathing pattern and patient anatomy introduce dose uncertainties in PT. Only in recent years, with the introduction of in-room CT and cone-beam CT (CBCT) for patient positioning, it has become feasible to monitor these variations without relying on external surrogates (Landry and Hua 2018). However, to make more use of the daily acquired CBCTs for daily 4D dose recalculations, 4D reconstruction and 4DCBCT-based 'virtual 4DCT' generation has yet to be established and to be implemented clinically. So far, the use of 4DCBCT for adaptive PT for lung cancer has been studied in silico (Veiga *et al* 2016). Also, in a phantom setting the feasibility of 4DCBCT-based proton dose calculation has been demonstrated (Niepel *et al* 2019).

Intra-fractional variations, occurring during beam delivery, still can only be monitored by external surrogates and thus remain largely undiscovered. The broader clinical implementation of fluoroscopy during beam on might give intra-fractional insights using internal surrogates (Shirato *et al* 2012). Future developments towards combined MR-PT machines might enable full 4D online monitoring.

4D optimized planning. 4D optimized planning has recently become available in commercial TPSs (Engwall *et al* 2018). Several studies have shown that the incorporation of respiratory motion, along with setup and range uncertainties, into 4D robust optimization, has the potential to improve the resilience of target and normal tissue dose distributions in PBS-PT plans in the face of the uncertainties considered (Liu *et al* 2016, Cummings *et al* 2018, Ge *et al* 2019). However, 4D optimized planning remains computationally expensive and time consuming, requiring further developments to make it more widely usable in clinical routine (Pepin *et al* 2018). Furthermore, the impact of different deformable image registration (DIR) algorithms (Ribeiro *et al* 2018) and the physical correctness of dose accumulation remain topics of concern for 4D optimized planning (see article on 'Treatment Planning').

4D evaluation. Papers addressing the robustness evaluation of PBS-PT plans for moving indications mainly report on the impact of setup and range errors, breathing motion and interplay individually. Only recently also studies on the combined impact of different uncertainties have become available (Inoue *et al* 2016, Ribeiro *et al* 2019). These comprehensive 4D robustness evaluation methods are essential to safely extend PBS-PT to moving indications. They allow the assessment of full PBS-PT treatment courses for moving targets, helping to define optimal clinical protocols for this group of patients.

4D delivery/motion mitigation. While in a research context all kind of sophisticated motion mitigation approaches like phase-correlated rescanning (Ogata *et al* 2014), multi-gating (Graeff *et al* 2014) or tracking (Zhang *et al* 2014) have been discussed, the vast majority of PBS-PT centers treating moving indications relies on simple motion mitigation approaches. It has been stated that for motion amplitudes <5 mm rescanning might be sufficient to assure robust treatments of moving targets (Molitoris *et al* 2018). For larger motion amplitudes techniques are preferred that reduce the motion extent. Respiratory gating and breath-hold techniques are theoretically desirable but logistically challenging, especially in large centers with a single proton source/accelerator and multiple treatment rooms and in patients with poor lung function. While still being investigated, the use of mechanical ventilation, may be a promising way forward for the delivery of PT (Molitoris *et al* 2018, van Ooteghem *et al* 2019).

4D adaptive therapy. During the course of fractionated radiotherapy, deformational and mass changes associated with regression of the visible tumor occur frequently. These changes often also affect the motion

characteristics of the tumor and the surrounding tissue. Prospective pretreatment evaluations only provide multi-scenario predictions without giving a clear patient-specific conclusion for the actual PBS-PT treatment. To provide robust treatments, especially with highly sensitive PT, adaptive workflows have been suggested (Chang *et al* 2017).

To facilitate treatment quality evaluation and to support decisions regarding plan adaptation, fraction-wise retrospective 4D dose reconstruction and accumulation aiming at the evaluation of treatment quality during and after treatment has been implemented (Meijers *et al* 2019). The described approach considers the influence of changing patient anatomy and variations in the breathing pattern by using treatment delivery log files and breathing pattern records of each fraction as well as most recent available imaging information to reconstruct and accumulate the actual delivered 4D dose. Treatment delivery log are produced by the treatment delivery system and contain, among other data, information about spot position, monitor units (MU) and energy.

Advances to meet the challenges

With the capabilities of new combined imaging and delivery machines (MR-LINAC), the photon therapy world is about to implement daily adaptive treatment regimens (Hunt *et al* 2018, Beaton *et al* 2019, Corradini *et al* 2019) while in PT still rarely more than two or three adaptations are applied throughout the whole treatment course (Mohan and Grosshans 2017, Mohan *et al* 2017). Time-consuming manual step-wise treatment workflows, the inflexibility of commercial PT equipment (including the treatment planning and oncology information software) and the high diversity in the PT landscape currently prohibits to move towards daily (real-time) or even online (during beam delivery) 4D adaptive treatment approaches. The automation of workflows will play a key element in the further enhancement of 4D planning and delivery of PBS-PT. To make adaptive workflows sustainable, also a broader employment of hypofractionated treatment regimens might be required (see article on 'Efficient Treatment Room Utilization').

Imaging capabilities at PT facilities have significantly improved over the last years. CT imaging has been the standard for many years. New PT facilities are often equipped with in-room or near-room CT scanners enabling smooth repeated CT workflows. In the context of daily or online 4D adaptive treatments, daily (or continuous during beam delivery) 4D imaging is required. That cannot be achieved via CT due to the imaging dose. CBCT and MR imaging might be alternatives in this case. While CBCT has been an established technique in photon treatment rooms for almost two decades, the widespread adoption of volumetric IG in particle therapy is recent (Landry and Hua 2018). Onboard MR guidance for particle therapy is currently not commercially available but is being actively investigated. A recent review paper (Oborn *et al* 2015) predicted the accelerated development of hardware and simple prototype systems within a few years and coupled systems integrated with gantries in a decade. To achieve online 4D imaging and subsequently (online) 4D adaptive PBS-PT with either modality, CBCT or MR, further developments are required. (see articles on 'IG' and 'Adaptive Therapy').

Automatic synthetic CT (sCT) generation. Neither CBCT nor MR scans are suitable for proton dose calculations. The clinical implementation of daily or online 4D adaptive PBS-PT will rely on the establishment of automated methods to generate sCTs based on CBCT or MR. Especially promising in this context are approaches based on deep learning techniques.

For CBCT deep learning based sCT generation approaches have been investigated (Kida *et al* 2018). However, for 4D applications, only DIR-based sCT generation methods have been investigated (Veiga *et al* 2016, Niepel *et al* 2019) with minor focus on the automation.

Also, sCT generation based on MR images has been investigated for MR-based PBS-PT (Maspero *et al* 2017, Guerreiro *et al* 2019). There are no papers yet on 4D MR-based PBS-PT employing deep learning sCT generation approaches with a high level of automation.

Automatic image processing. Automation will also play a major role in contouring for 4D adaptive PBS-PT. Manual delineation on 4DCT is resource intensive due to the high volume of data, which results in longer contouring duration and uncertainties in defining the target. A recent review concluded that auto-contouring for lung tumors is reliable and efficient, producing accurate contours with better consistency compared to manual contours (Wong Yuzhen and Barrett 2019). However, manual inputs were still required both before and after auto-propagation.

Automatic QA. With the employment of 4D adaptive PBS-PT treatment regimens PSQA workflows also must become more efficient. The current clinical practice of experimental validation of individual fields will have to be replaced by automated simulations using treatment planning steering files or machine log files and a MC code as independent dose calculation engine (see article on 'Treatment Planning'). Concepts towards effective and

efficient patient-specific QA for PT have been developed by several groups (Zhu *et al* 2015, Matter *et al* 2018, Winterhalter *et al* 2018).

Concluding remarks

A paradigm shift from manual stepwise to automatic seamless and flexible treatment approaches is required for the clinical implementation of real-time or even online 4D adaptive PBS-PT. 4D imaging (also see section on 'Improving imaging') for treatment planning, 4D treatment planning, 4D QA and 4D treatment verification must be integrated into a real-time 4D adaptive PBS-PT treatment loop to achieve significant improvements in the treatment of mobile cancer indications.

12. Considering the RBE of protons

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Status

Currently tumor prescription doses and OAR constraints in PT are based on a generic and constant RBE of 1.1 to normalize the physical dose to a photon equivalent. Prescription doses are reported as Gy(RBE). The value of 1.1 was chosen in the early days of PT based on measured RBE values *in vivo* relative to Co^{60} in the center of the target volume at $\geqslant$2 Gy per fraction for various endpoints such as skin reaction and LD_{50}. It was chosen conservatively to ensure target coverage with prescriptions based on photon experience. Based on an analysis of all published cell survival data *in vitro* fitted with the linear-quadratic dose response curve (with parameters α and β), the estimated average RBE is about 1.15 in the center of a typical spread-out Bragg peak (SOBP) at 2 Gy(RBE) per fraction (Paganetti *et al* 2002, Paganetti 2014). Aiming at a conservative RBE for tumor control, this is in line with the clinical use of 1.1 if an average RBE is to be applied for the target and if clonogenic cell survival *in vitro* serves as a surrogate for tumor cell kill. For normal tissue the RBE can be substantially higher (Paganetti 2014), which is currently neglected in treatment planning. Elevated RBE values can be expected particularly at the end of range where the LET is increasing when protons decelerate.

Our current knowledge on variations in RBE is largely based on measurements of clonogenic cell survival *in vitro*. Figure 7 shows a fit through the majority of published experimental data. Various RBE values for endpoints other than cell survival have also been measured *in vitro* and *in vivo* but results are inconsistent.

RBE studies based on patient data are inconclusive due to limited data sets and generally low toxicity incidents. There is however increasing concern that proton RBE for normal tissue injuries may be underestimated significantly, leading to unexpected toxicities (Haas-Kogan *et al* 2018). There is anecdotal evidence that toxicities seen with protons might be more severe but not more frequent compared to photon therapy. A potential explanation is that patient variability is magnified by RBE effects (Paganetti 2017).

A Task Group report by the AAPM from 2019 concluded (Paganetti *et al* 2019):

- The current clinical practice of using a constant RBE for protons should generally be maintained but specific clinical scenarios warrant a change in current practice.
- It is important to acquire clinical data to allow the reconstruction of RBE doses and correlate with clinical outcome in both prospective and retrospective studies.
- There are sites and treatment strategies to be identified where variable RBE might be safely utilized for clinical benefit.
- The PT community needs to assess the potential clinical consequences of delivering biologically weighted doses based on LETd and/or RBE and as a function of dose and biological endpoints and assess the potential for harm and benefits associated with the clinical implementation of variable RBE and dose-weighted LETd models into TPSs.
- Experiments are needed to improve our current understanding of the relationships among *in vitro*, *in vivo* and clinical RBE and develop recommendations to minimize the effects of uncertainties associated with proton RBE for well-defined tumor types and critical structures. Given the clinical practice of multi-modality treatments, RBE experiments using radiation-drug combinations are needed as well.

A retrospective qualitative and quantitative analyses of late-phase lung-density changes (indicative of asymptomatic fibrosis) for a small cohort of breast cancer patients irradiated to the chest wall showed that late-phase asymptomatic radiographic changes in the lung are associated with a proton RBE potentially even exceeding 3.0 (Underwood *et al* 2018) for 2 Gy/fraction. In contrast, for the same endpoint, an RBE on the order of 1.1 was deduced in a cohort of hypofractionated (SBRT) lung cancer patients even though differences in the time course of the inflammatory response after proton compared to photon SBRT were seen (Li *et al* 2019b). A study on rib fractures in breast cancer patients indicated elevated RBE values at the end of range similar in magnitude compared to clonogenic cell survival data (Wang *et al* 2020).

Toxicities are a major concern particularly for pediatric patients but it is unclear if RBE variations have a clinical impact (Indelicato *et al* 2014, Sethi *et al* 2014). The potential impact of LET or RBE on brainstem necrosis in patients has been analyzed (Peeler *et al* 2016, Eulitz *et al* 2019). Unfortunately, most studies do not consider the correlation of voxels from the same patient as well as the fact that high LET regions are typically in the

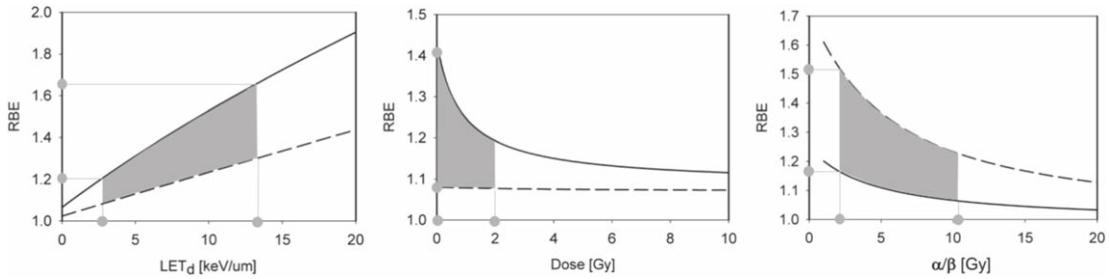

Figure 7. Proton RBE for clonogenic cell survival as predicted by an empirical model (McNamara, Schuemann *et al* 2015). Left: RBE as a function of LET_d at 2 Gy for $(\alpha/\beta)_x = 2$ Gy (solid) and 10 Gy (dashed). Middle: RBE as a function of dose for $LET_d = 2.5$ keV μm^{-1} for $(\alpha/\beta)_x = 2$ Gy (solid) and 10 Gy (dashed). Right: RBE as a function of $(\alpha/\beta)_x$ for a photon dose of 2 Gy and LET_d values of 2 keV μm^{-1} (solid) and 10 keV μm^{-1} (dashed). The gray areas and projection lines highlight the clinically most relevant regions for standard fractionation. $(\alpha/\beta)_x$ refers to the ratio of α and β for the x-ray dose-response curve.

periphery of the target where high doses will also increase the likelihood of toxicities. In fact, when patients were analyzed individually, no correlation of elevated RBE in necrotic regions was seen in a cohort of 50 adult patients (Niemierko *et al* 2021).

Current and future challenges

While of limited value for establishing RBE values in patients, *in vitro* studies still offer valuable information to our understanding of the basic biological responses to proton and photons radiation. Challenges remain on how to standardize measurements to allow inter-institutional comparison and to limit the large uncertainties in reported data (Durante *et al* 2019).

There are currently significant uncertainties in proton RBE values, particularly for *in vivo* endpoints. Human tumor responses can be measured *in vivo* using measurements such as the dose for 50% local control of the tumor using human tumor cells implanted in immune-deficient animals but translation into the clinic is questionable. As for patient data, it is unlikely that toxicity data from single institutions will suffice to define RBE for normal tissue endpoints. Due to the uncertainties in RBE, treatment plan optimization based on RBE models is not feasible with clinically acceptable accuracy as patient variability is likely in the same order of magnitude as RBE variations and uncertainties.

Considering typically lower α/β values in healthy tissues, at least for cell survival, as well as lower doses than in the target, one might expect larger RBE values for normal tissue. One reason for our difficulty to assess RBE effects in critical structures from clinical data is the difference in dose distributions after photon and proton irradiations. Most outcome studies are based on normal tissue complication probability (NTCP) models that are mainly based on dosimetric indices extracted from dose-volume histogram (DVH) data (see articles on 'Selection of Patients' and 'Outcome Modeling'). As proton dose distributions in normal tissue are typically more heterogeneous, estimation of RBE (defined for the same level of effect in a homogeneous area of dose) is challenging.

A value of 1.1 seems appropriate for the tumor if one aims at a conservative value. But RBE depends not only on factors such as fractionation and LET, but also the genomic characteristics of human cells. An important barrier to assessing the biological effects of PT clinically is the paucity of predictive biomarkers (Willers *et al* 2018). Individualized dose prescriptions are desirable, not only in proton but also in photon therapy. (See article on 'Biomarkers'.)

Advances to meet challenges

Even though uncertainties in RBE impacts both, tumor control as well as NTCP, one might expect a bigger clinical impact on NTCP because 1.1 was chosen conservatively. Nevertheless, moving forward, incorporating RBE variations in treatment planning could impact tumor control probability (TCP) as well. In general, the impact is driven by the steepness of the dose-response curve in the region of interest.

Identifying patients that most benefit from protons (see article on 'Selection of patients for PT') should include not only dosimetric but also biological markers identifying individual patients with, for example, high tumor RBE. For instance, a subset of human cancers are expected to show defects in DNA repair pathways that may influence the RBE (Rostek *et al* 2008, Grosse *et al* 2014, Liu *et al* 2015). Additional studies on genomically characterized human cancer cell lines and normal human tissue would be valuable.

One has to keep potential RBE variations amongst patients in mind when comparing doses in clinical trials or when analyzing toxicities and tumor recurrences. With a continued use of a constant RBE the interpretation of

outcome data might be misleading when tissue- and spatially variant RBE variations are neglected (Paganetti 2017, Chen *et al* 2018).

In order to move towards a true understanding of RBE values in patients, the analysis of outcome data using blood and imaging biomarkers is urgently needed (see article on 'Biomarkers'). Particularly for healthy tissue, retrospective investigations on toxicity are currently based on limited number of patients. Furthermore, dose-response relationships should ideally not be solely analyzed based on organ contours but on sub-regions or even voxel-based (Palma *et al* 2019a, 2019b). Moving forward, machine-learning techniques will be a powerful tool particularly when trying to identify radiosensitive sub-regions in organs utilizing the different dose distributions from protons and photons.

Ideally, TPSs would incorporate RBE models and optimize based on RBE-weighted doses. However, as discussed above, our knowledge on mechanisms of normal tissue toxicity prevents this for the foreseeable future. Ongoing efforts on implementing models into treatment planning programs will help estimate potential effects but such models may not be ready for plan optimization.

IMPT allows the delivery of inhomogeneous dose distributions for each field causing plan degeneracy (Lomax 1999). As a consequence, LET distributions can be influenced in IMPT without significantly altering the dose constraints in treatment planning, i.e. dosimetrically equivalent plans can show differences in LET distributions (Grassberger *et al* 2011, Fager *et al* 2015, Unkelbach and Paganetti 2018). This can be utilized to decrease the efficacy of PT in certain regions of normal tissue, allowing biological dose optimization despite uncertainties in RBE values (Unkelbach *et al* 2016). Translating this method into clinical routine will be beneficial for many patients. The method is largely insensitive to organ and patient specific variations in RBE but, depending on the number of fields, works better for normal tissue than for tumors.

Concluding remarks

A constant RBE of 1.1 is an appropriate average value for ensuring tumor control. However, particularly at the end of range, RBE values are likely higher, potentially affecting normal tissue toxicities. Understanding the difference between photon and proton radiation is now of critical importance because treatment planning vendors may start to prematurely offer RBE based treatment planning using models based clonogenic cell survival data.

Whilst useful in modeling and for understanding biological mechanisms, neither *in vitro* nor animal experiments will ultimately resolve the issue of how proton RBE should be incorporated clinically for personalized treatment planning. The paucity of clinical evidence indicates that RBE variations maybe on the same order than variability in patient radiosensitivity. Retrospective and prospective outcome studies have to be prioritized. PT, with its typically more heterogeneous dose distributions compared to photon therapy allows better understanding of volume effects in OAR (see article on 'Outcome Modeling'). Analyzing proton patients will thus also benefit outcome modeling for conventional treatments.

In the meantime, LET based optimization techniques should be implemented clinically as they allow judging treatment plans based on dosimetric indices while likely reducing the risk for normal tissue toxicities.

Part 3: Improving imaging

13. Advances in imaging for proton treatment planning

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Status

X-ray CT is the undisputed primary imaging modality for proton treatment planning, specifically for dose calculation. The basic methodology, namely the conversion of CTN derived from a native single-energy CT (SECT) into a quantity relevant for dose calculation (usually the stopping-power ratio, SPR) using a heuristic conversion function (Hounsfield look-up table, HLUT), has kept unchanged since the pioneering years of clinical PT. Nevertheless, in the past decade relevant improvements in CT imaging were introduced (Wohlfahrt and Richter 2020). With iterative reconstruction techniques image noise can be clearly reduced, bearing substantial potential for dose reduction. Still, they have not yet found their way in broad clinical use. In contrast, automated tube current adaptation during acquisition with respect to the patients' anatomy is widely applied, allowing for a constant noise level over different CT slices and effectively reducing imaging dose.

For improved tumor delineation and staging, complementing contrast-enhanced SECT scans and/or positron emission tomography (PET) and magnetic resonance imaging (MRI) are utilized depending on the target. As PET or MRI scans are often performed at different scanners and time points, additional challenges arise from deviations in patient positioning and the required involvement of image registrations.

Notably, CT imaging and CTN-to-SPR conversion protocols vary largely between centers as well as the acquisition and processing of multimodal imaging, introducing severe inter-center variations in dose calculation and delineation (Vinod *et al* 2016a), potentially interfering with the outcome of multi-centric clinical trials.

Current and future challenges

The reduction of the uncertainty in CT-based SPR and range prediction is a major challenge. The limitations of the HLUT approach are the dominant cause of the nominal range uncertainty in treatment planning which has remained practically unchanged over decades with 3%–3.5% of the absolute range (Taasti *et al* 2018). This is not unfounded, as a recent inter-center comparison, conducted within the European Particle Therapy Network, revealed a 2.6%–2.9% variation in range prediction. For other imaging modalities, like MRI or CBCT, the range prediction accuracy is inferior to CT, currently prohibiting their application for proton treatment planning. Still, with appropriate and required improvements, they could potentially be used in adaptive workflows, as long as the uncertainty in range prediction is smaller than the detected treatment deviation.

An overarching challenge in pre-treatment imaging is an appropriate tissue differentiation, being important not only for accurate SPR assignment, but also for tumor and OAR segmentation in general.

We define the following long-term goals, which would lead to relevant improvements:

- Range prediction accuracy $\leqslant$1% with CT-based imaging
- Automated tissue differentiation for segmentation and appropriate SPR assignment for non-CT imaging
- General improvements in target and OAR delineation, e.g. using different, purpose-tailored image contrasts and artifact reduction techniques
- Reduction of inter-center variability in SPR prediction and delineation.

Advances in pre-treatment imaging to meet challenges

The clinical availability of DECT scanners in radiology has enabled various applications to improve the diagnostic efficiency and efficacy within the last 15 years and is now often common practice (Agrawal *et al* 2014). Despite the large research interest in radiation oncology, the first use of DECT for routine proton treatment planning was realized in 2015. Its widespread clinical implementation will become apparent in the near future with increasing evidence for its benefits especially for PT.

Due to a better material differentiation with DECT and thus incorporation of intra- and inter-patient tissue variations, current intrinsic limitations in CT-based stopping-power prediction using an HLUT can be clearly

diminished. A relevant reduction of the current range uncertainty of 3%–4% to below 2% has already been proven to be clinically feasible with DECT-based direct SPR prediction (Wohlfahrt and Richter 2020) and might be further decreased by improvements in post-processing algorithms (beam hardening and scatter correction, patient size estimation, image smoothing and de-noising). Efforts of CT vendors to provide SPR datasets as input for dose calculation together with dedicated calibration of their CT systems would clearly facilitate the clinical workflow and contribute to a desirable standardization to reduce the current large inter-center variations.

Furthermore, the generation of virtual monoenergetic images after CT acquisition provides different image contrasts—low energy (40–60 keV) for increased soft tissue contrast or high energy (120–200 keV) to reduce metal artifacts. Separating the distribution of contrast agents in images can further contribute to a better tumor visibility and might even serve as a measure of organ functions or tumor metabolism (functional imaging). The assessment of the optimal application and resulting potential benefit of such additional information for target and OAR segmentation is currently limited and needs to be comprehensively addressed in future studies.

Nowadays, several DECT acquisition techniques exist (dual-source, dual-layer, fast-voltage switching, dual-spiral). Each of them offers specific benefits and also disadvantages in terms of energy separation, tube current modulation, field of view as well as spatial and temporal differences in projections. Hence, no DECT device for general-purpose application in radiation oncology currently exists and a compromise has to be made based on the respective objective and individual requirements (Wohlfahrt and Richter 2020, van Elmpt *et al* 2016).

Photon-counting CT systems, the expected next-generation CT technology with energy-resolving detectors, will potentially overcome the mentioned technical limitations of current DECT techniques due to a spectral separation in several energy bins after CT acquisition while maintaining full temporal resolution. Hence, the accurate direct SPR prediction methods developed for DECT will also be unconditionally applicable for body regions with motion-induced anatomical changes. Moreover, projection-based corrections for beam hardening and scattering are thus unconditionally feasible. The availability of multi-dimensional attenuation information (diverse combination of energy bins) seems promising to improve material differentiation, which potentially leads to a higher tissue contrast for tumor and organ segmentation and differentiation of multiple contrast agents. In initial proof-of-concept studies, first prototypes have shown a comparable or slightly better accuracy in SPR prediction and material classification than DECT. Further improvements in spectral de-noising techniques might also reduce the current restrictions in the selection of an appropriate number of energy bins due to unacceptably high image noise. Photon-counting CT can thus become an emerging alternative to DECT in radiation oncology (Willemink *et al* 2018).

Range probing, comparing measured and expected depth dose after patient transmission, is a promising tool to verify CT-based range prediction and eventually adapt the CTN-to-SPR conversion (Parodi 2020). Its widespread clinical application would require a smooth integration in PT systems.

The acquisition of three-dimensional stopping-power information using proton CT has been an active focus in research for decades, resulting in first experimental prototypes, which are still in an early stage of development. With the ongoing improvements and clinical implementations of DECT or photon-counting CT, the potential additional gain in SPR accuracy from proton CT becomes smaller and might be not even clinically relevant at some point. Proton CT would also come with considerable additional costs, would only be applicable for a limited number of body regions due to the current restriction in maximal proton energy (roughly 230 MeV) at most centers, and would reduce the number of patient treatments caused by long acquisition times (several minutes) in the proton treatment room (Johnson 2018). A better scatter prediction already clearly improved the proton CT image quality, but physical constraints limit further improvements in spatial resolution at high-density material gradients and resulting ring and streak artifacts (Parodi 2020). Potential use cases could be patients with metal implants close to the treatment volume (Johnson 2018). However, the continuous improvement of artifact reduction techniques in (multi-energy) x-ray CT could be the clinically sufficient and more cost-effective alternative.

MRI offers a broad variety of acquisition modes to differentiate soft tissues and to assess their functional behavior. Combining multi-modality imaging including MRI has proven to reduce intra- and inter-observer variability in delineation (Vinod *et al* 2016b). The robustness and accuracy of MRI-based material assignment (e.g. sCT generation) for SPR prediction could potentially be improved by using DECT or even proton CT instead of SECT as input. Improvements in geometrical accuracy, motion detection and management as well as accuracy and precision of quantitative MRI are ongoing research challenges (Das *et al* 2019). Hence, synchronized multi-modality imaging in treatment position is worth aspiring to combine the respective advantages of each technique, decrease registration errors and maximize the patient-specific tissue information available for treatment planning.

Moreover, the technological achievements in imaging enable an accurate and precise experimental determination of the mean excitation energy in biological tissue samples and patients by combining DECT and range probing or proton CT, respectively. A combination of MRI and DECT or even photon-counting CT can facilitate an even better *in vivo* material differentiation and characterization compared to a single-modality approach.

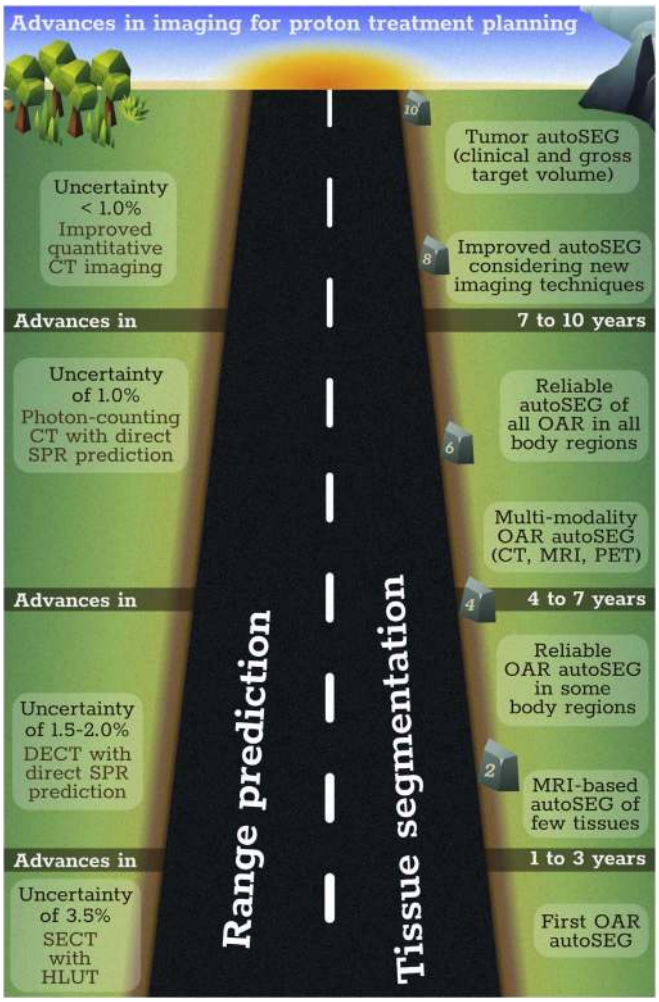

Figure 8. Potential advances in imaging for proton treatment planning, starting from the current situation (bottom). They can be grouped in two tracks—improvements for range prediction accuracy and improvements for tissue segmentation. The proposed periods correspond to the broad clinical application of the respective techniques. (autoSEG = auto segmentation).

Concluding remarks

The field of pre-treatment imaging has gained substantial translational research interest. DECT, offering substantial reduction of range uncertainty, is currently at the critical cornerstone of broad clinical implementation. In terms of range accuracy, it will set the benchmark for other techniques. Therefore, photon-counting CT will potentially bring benefits for segmentation from tailored image contrasts and enabling direct SPR prediction, as introduced with DECT, for a broader patient population (motion-influenced regions) rather than further decreasing range uncertainties substantially. The investigation and tailoring of photon-counting CT for PT requirements will thus be an exciting field of translational research. For PT applications of all imaging modalities, quantitative imaging in clinical realistic scenarios is key and should be considered in calibration and validation studies, e.g. using phantom setups covering different clinical scenarios.

In summary, we are confident, that not one single imaging modality will fulfill the broad spectrum of radio-oncological needs. Hence, research efforts should focus on finding the best multi-modal synergies. Bringing together imaging and radiation oncology expertize is thus becoming more and more crucial. Figure 8 outlines potential advancements in the next few years.

Conflict of interest statement

The authors received individual funding as lecturer from Siemens Healthineers (2018), which was not related to this study. OncoRay has an institutional research agreement with Siemens Healthineers in the field of DECT for particle therapy (2016–2020) as well as an institutional agreement as reference center for DECT in radiotherapy and a software evaluation contract. For the present paper, the authors received no financial support. The other authors report no conflict of interest.

14. Image guidance

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Image guided Radiotherapy for improved position verification

In modern radiotherapy, both photon and PT, there is a huge need for imaging; we will argue that the roadmap for IG in PT is heavily affected by the experiences in the photon therapy. Image guided radiotherapy (IGRT) is a long standing research and clinical innovation area (Verellen *et al* 2007). Imaging in radiotherapy has mainly been developed for improving position verification, that is, to validate the anatomy on the treatment couch relative to the anatomy during treatment planning. The more precise position verification during fractionated radiotherapy treatments, the more conformal dose distributions to the target can be enabled, sparing surrounding healthy tissue from unwanted dose.

A host of imaging modalities is being applied while also surrogates for imaging the target, e.g. using nearby bony anatomy or fiducial markers (Nederveen *et al* 2003), are (and can) be used. Most prominent in IGRT is the development and clinical introduction of CBCT acquired from a patient in the actual treatment position (Jaffray *et al* 1999). Such volumetric data enables much more precise target identification and with that, patient positioning and is currently in widespread clinical use (Qin *et al* 2015).

Recently, in the photon therapy arena, integrated MRI radiotherapy systems were clinically introduced (Mutic and Dempsey 2014, Raaymakers *et al* 2017). These systems enable MR imaging of patients in the actual treatment position, providing unrivaled, volumetric, soft-tissue contrast data for position verification. If desired, this can be continued during dose delivery for continuous patient monitoring.

Imaging in radiotherapy for treatment adaptation

The drive for improved imaging during radiotherapy originates from the need for better position verification and has led to daily, volumetric data of the patient from the treatment table. The advent of daily volumetric imaging also led to adaptive radiotherapy (ART; see also article on 'Adaptive Therapy'), as by using the daily data the treatment margins can be re-evaluated (Yan *et al* 1997a, 1997b). But also, it enables generation of a new treatment plan to account for anatomical changes, e.g. Marchant *et al* (2018), instead of trying to re-position the patient according to the pre-treatment planning. Also for such daily treatment adaptation, the hybrid MRI radiotherapy systems will raise the quality of images for clinical decision making on the necessity of adapting. And with their capability to also provide repeated MRI data during dose delivery will drive towards intra-fraction plan adaptation and ultimately real-time adaptive radiotherapy (Kontaxis *et al* 2015). Currently, online, or more specifically daily, MRI based adaptation is an accepted clinical reality (Henke *et al* 2018).

Also, recently a new AI driven eco-system for adaptive photon beam therapy is commercially launched for clinical introduction (www.varian.com/ethos). This workflow uses CBCT as an input, so it lacks the soft-tissue contrast of MRI, but it provides an integrated, fast, adaptive workflow, which enables 15 min full adaptive radiotherapy treatment fractions for certain tumor sites.

Which imaging modality will be most suitable for which tumor site, the frequency of adaptation and the delivery on the promise that this will lead to more hypo-fractionation needs to be established from clinical experience. The desire for improved position verification and more frequent treatment adaptation will jointly require better, and more frequent, imaging.

Roadmap for IG in PT

The introduction of the imaging and adaptive innovations has mainly taken place in the photon therapy clinic, widespread adoption in PT is lagging for these developments (Lomax 2018). For PT both position verification and treatment adaptation are very relevant for improving treatment accuracy. IGRT developments from photon beam therapy are being translated to PT, e.g. CBCT guidance is being used more and more frequently in PT (Landry and Hua 2018). In essence the roadmap for imaging in PT, where it concerns anatomical imaging for position verification and for adaptation, is similar to that of photon therapy. A nuance is that PT is considered high-end radiotherapy, both due to its ability to stop the treatment beam posteriorly of the tumor to spare the surrounding tissues and due to its costs. To live up to this expectation, imaging in PT should be at least of similar quality as the state-of-the-art imaging used in photon beam therapy. This implies that the roadmap should aim to obtain real-time, volumetric, high soft-tissue contrast imaging to enable position verification, dose reconstruction and treatment adaptation as MRI provides for photon beam therapy.

An additional requirement for imaging in PT is to verify not only the geometrical location of the target, but also the proton beam range in the patient (Knopf and Lomax 2013). Proton radiography (Hammi *et al* 2018),

PET imaging (Parodi *et al* 2007) and prompt gamma imaging (Hueso-González *et al* 2016) are being explored for treatment verification (see also article on '*in vivo* range verification').

Thus, patient imaging during treatment initialization, when the patient is on the treatment table, should yield both the anatomical and stopping power data (see also article on 'Advances in imaging'). For PT both topics are active fields of research (Poludniowski *et al* 2015, MacKay 2018). Alternatively, these imaging data can be used for plan adaptation (see also articles on 'Adaptive Therapy' and 'Treatment planning'). By combining the data, the stopping powers of the various tissues in the anatomy can be determined, while all relevant structures for (re-)planning can be identified on the anatomical data. Once this is done, the challenge of re-planning is very similar as for photon beam therapy, of course with the difference being a PT TPS, for instance by daily CBCT based re-planning. For PT, daily CBCT has recently become a clinical reality while *in vivo* range determination by prompt gamma imaging is awaiting wider clinical employment and investigations. So daily CBCT based plan adaptation is something that can be explored currently. However, to match the state-of-the-art image quality in photon beam radiotherapy, MRI for anatomical imaging should be on the roadmap.

MRI guided PT

In MRI guided PT, the need for stopping power data is still equally much needed as with any other anatomical image guided modality. If the stopping power data is coupled to the MRI, the repeated, ultimately real-time, anatomical data can be used to track the entire anatomy during beam delivery. Actually, for PT, with its sharp dose fall off around the Bragg peak, this might be even more relevant than for photon beam therapy. MRI guidance in the context of PT has been proposed (Raaymakers *et al* 2008) and is being explored experimentally (Schellhammer *et al* 2018) and *in silico* (Oborn *et al* 2017). This is not near clinical reality, still, as these developments to realize real-time adaptive MRI guided dose delivery in photon beam therapy are advancing, this should be on the roadmap for PT too.

Concluding remarks

On-line adaptive radiotherapy is a new clinical reality in the photon radiotherapy world. Volumetric anatomical imaging in treatment position as well as a transition to more seamless, automatic workflows enables the clinical deployment of online adaptation. For PT to keep up with this reality, the road map should include *in vivo* range determination by prompt gamma imaging and volumetric anatomical imaging of the patient in treatment position on the treatment table. CBCT is a good starting point for improving position verification and daily plan adaptation.

MRI should be on the roadmap as it provides unequaled anatomical imaging for position verification but also anatomical tracking of both target and all surrounding structures. These features will drive a paradigm shift in photon beam radiotherapy towards online, and ultimately real-time, adaptive radiotherapy, something that will also affect the expectation of PT. A starting point for using MRI in PT is to include more MRI in the preparatory phase of treatment planning to investigate the coupling of range imaging and MRI.

Conflict of interest

Bas Raaymakers received financial research support from Elekta A B, Sweden for work on developing MRI guided photon therapy.

Part 4: Improving patient selection

15. Model-based selection of patients for PT

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Status

Beginning 2018, PT has been clinically introduced in the Netherlands. In 2015, the Royal Netherlands Academy of Arts and Sciences (KNAW) concluded that an RCT (randomized controlled trial) is not always the most optimal study design for evaluating the benefit of technology and that for different types of new applications, different research approaches are required (Langendijk *et al* 2018). Alternatively, for the selection of patients for PT, the so-called model-based approach was introduced, which has been accepted by the National Health Care Institute (ZiN) (Langendijk *et al* 2013, Widder *et al* 2016). Consequently, when adult patients are selected according to a model-based selection procedure, PT is insured care and will be fully reimbursed.

Model-based selection is developed to identify patients that may benefit from PT in terms of reducing radiation-induced side effects. It relies on three basic principles: (1) the definition of the target volumes and fractionation schedules is similar to what would be used when patients are with photons, assuming equivalent tumor control; (2) the dose to the most relevant OAR in the proton treatment plan should be lower than that obtained with photons (i.e. ΔDose), and: (3) this ΔDose should translate into an expected decrease in normal tissue complication probabilities (i.e. ΔNTCP). To translate ΔDose into ΔNTCP, NTCP-models are used, i.e. prediction models that describe the relationship between the dose distribution in OAR and ` risk on radiation-induced toxicity.

For each tumor site, the criteria for model-based selection are described in detail in National Indication Protocols for PT (NIPP), which contain general eligibility criteria (e.g. curative treatment), a detailed description of the NTCP-models that can be used for model-based selection as well as the ΔNTCP-thresholds to determine if patients qualify for PT. To assess ΔNTCP, an in-silico plan comparison is performed comparing the best dose distribution with photons with the best dose distribution with protons. Based on these dose distributions, NTCP-profiles for photons and protons and subsequent ΔNTCP are produced to assess if the criteria are met (figure 9).

For selection of head and neck cancer, three NTCP-models are used (moderate-to-severe patient-rated xerostomia, physician-rated dysphagia grade $\geqslant$2 and tube feeding dependence). For breast cancer patients, an NTCP-model for acute coronary events derived from the Darby model is used (Darby *et al* 2013).

Current and future challenges

Model-based selection requires high quality NTCP-models, preferably validated in independent datasets to test their generalizability of these NTCP-models (Langendijk *et al* 2018). However, for many tumor sites, the numbers of NTCP-models that meet these criteria is limited or are currently not available. E.g. the literature review on NTCP-models in low grade glioma patients did not reveal any NTCP-model that could be used for model-based selection. So far, these tumors, selection strategies should be applied. In the case of low grade glioma, selection is currently based on identifying patients with the most favorable prognosis (i.e. 5 years overall survival $>$50%) who are at risk for long-term neurocognitive decline. Second, virtually all NTCP-models published so far are based on photon-based radiation techniques. However, NTCP-models can be affected by changes in the irradiation technique. Therefore, it is paramount to continuously update and validate these NTCP-models in subsequent patient cohorts treated with new techniques. The challenge here is to create an infrastructure support for prospective collection of high quality data, allowing for development and validation of multivariable NTCP-models for comprehensive sets of radiation-induced toxicities.

Another important challenge is related to the clinical implementation. Model-based selection as part of routine clinical practice is completely new, relatively complex and resource intensive, especially if patients are referred from other centers. In head and neck cancer, approximately 30%–40% qualifies for PT based on the plan comparison, while in breast cancer this is only 5%–10%. Performing plan comparisons in all these patients is logistically not feasible. Therefore, tools to select patients in which a plan comparison is indicated are desperately needed.

Advances in science and technology to meet challenges

Along with the introduction of PT in the Netherlands, a nationwide PT research infrastructure (ProTRAIT) is currently under construction to support prospective data collection of all patients treated with PT. ProTRAIT aims to setup PT registries developing tools for radiotherapy that will enable an unprecedented combination of both DICOM-RT and clinical/follow up data for integrated analysis. More specifically, ProTRAIT: (1) defined tumor-specific registries for patient groups that are with PT; (2) setup an IT infrastructure supporting the model-based approach on a national scale by harmonizing data acquisition (clinical, DICOM RT); (3) makes data FAIR (Findable, Accessible,

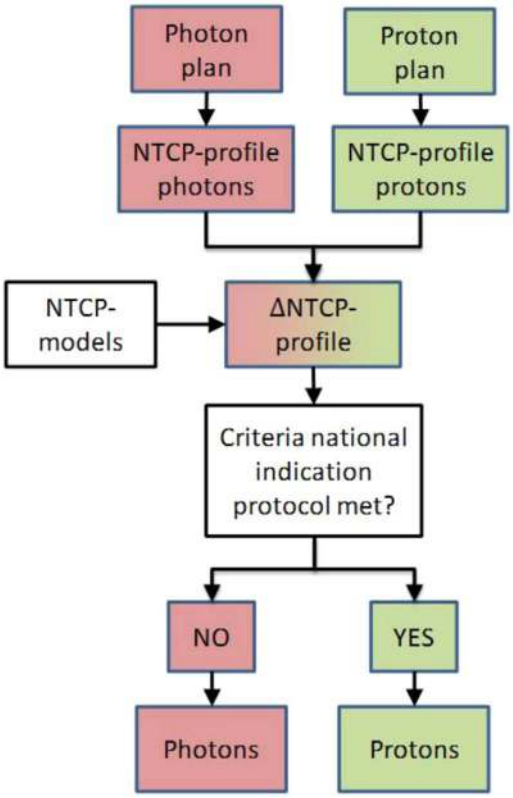

Figure 9. Schematic overview of model-based selection procedure.

Interoperable and Reusable) and links data from different sources and centers; (4) develops an IT infrastructure that supports fast development, update and external validation of NTCP models, and: (5) deploys an IT infrastructure to support QA in radiotherapy for clinical trials. This infrastructure will also be used for collecting data from photon-treated patients for the development and validation of NTCP-models. The ProTRAIT-project will be completed in 2021. This approach will be further extended on a European scale by the European Proton Therapy Network (EPTN).

To enhance further adoption of the model-based approach, clinical workflows need to be simplified and automated whenever possible. First, heterogeneity across centers in contouring OAR may jeopardize fair plan comparisons between photon and proton plans even when international guidelines are available (Brouwer *et al* 2015). Automated contouring using deep learning techniques derived from AI has emerged useful to improve performance resulting in smaller dose differences compared to manual contouring and marked reductions of delineation times (van Dijk *et al* 2020). AI solutions for automated photon-based treatment planning are currently developed and clinically deployed, holding the promise to significantly reduce treatment planning time while eliminating large variations in treatment planning performance across centers, as was recently shown in a Dutch benchmark study using predefined regions of interest in one patient (Verbakel *et al* 2019). Similar automated planning tools are under development for PT, however this is a more challenging task especially when combined with robust optimizsation (Kierkels *et al* 2019).

To reduce the number of unnecessary plan comparisons, attempts are made to use knowledge-based planning solutions (see article on 'Treatment Planning'), treatment planning based on prioritizing prescription goals or AI, to improve the accuracy of identifying patients who will qualify or not for PT prior to a plan comparison in different phases of the preparation workflow (Wilkens *et al* 2007, Delaney *et al* 2017). As validated NTCP models become available for various treatment sites and combined NTCP profiles start to be used, a transition from NTCP evaluation to NTCP evaluation and optimization becomes more feasible. This may further improve efficiency of clinical workflows.

Concluding remarks

In the Netherlands, patients are selected for PT using a model-based approach provided that PT is intended to reduce radiation-induced side effects with similar loco-regional control. The main challenge is to develop and validate multivariable NTCP-models to enrich ΔNTCP-profiles that can be used for patient selection for both photons and protons. To this purpose, a nationwide IT research infrastructure is created (ProTRAIT). In addition, clinical workflows should be optimized and automated to facilitate logistic hurdles in patient selection and referral.

16. Outcome modeling for PT

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Status

Both TCP as well as NTCP models are constantly being refined. As normal tissue sparing is one of the main dosimetric advantages of PT, it will likely not be tumor control but rather normal tissue complication differences compared to photon therapy that will determine its benefits. Several retrospective and prospective studies have identified areas where PT does indeed make a significant clinical impact and reduces toxicities but there are also studies where an advantage was not seen. Independent of the delivery method, PT reduces the integral dose (total energy deposited in the patient) by a factor of 2–3 compared to photon techniques (Lomax *et al* 1999). While this reduces the overall dose to healthy tissue, it may not translate into a toxicity advantage depending on the dose-limiting endpoints and how the dose is distributed.

Models based on parameters deduced from clinical studies are often used to predict clinical outcome (Semenenko and Li 2008). For instance in lung, single parameters are extracted from DVHs such as V20 and mean lung dose to predict radiation pneumonitis in photon therapy (Fay *et al* 2005, Marks *et al* 2010). However, dose volume parameters deduced from photon treatments might not apply to proton treatments with more inhomogeneous dose distributions (Tucker *et al* 2019). For instance, dose to the lower parts of the lung is more predictive of radiation pneumonitis than dose to the upper lobes (Seppenwoolde *et al* 2004, Hope *et al* 2006).

PT outcome relative to photon therapy is also affected by RBE considerations (see article on 'RBE'). The current RBE formalism assumes that NTCP estimates for PT can be based on scaled photon doses in each CT voxel. There is increasing concern that the RBE for normal tissue injuries may be underestimated, leading not only to more but to more severe toxicities than expected from analyzing dosimetric indices (Haas-Kogan *et al* 2018). Toxicities in PT could be more affected by inter-patient variations leading to a wider distribution of the severity compared to photon radiation (Paganetti 2017), which would also impede comparisons between cohorts. Predicting *in vivo* normal tissue responses after radiotherapy using *in vivo* cellular biomarkers and radiosensitivities assumes a direct correlation of toxicity with radiation induced DNA damage, neglecting, for instance, the involvement of cytokine-mediated multicellular interactions in radiation response (Stone *et al* 2003). As discussed in the roadmap article on Systemic Effects in PT, the integral dose may even influence toxicities via impacting immune response.

Current and future challenges

Most outcome studies apply NTCP models that are based on dosimetric indices extracted from DVH data. Even more simplistic and thus complicating IMRT/IMPT comparison, the majority of current approaches for modeling of radiation dose-response rely on single parameters such as mean dose or generalized effective uniform dose to an OAR represented by a single segmented (contoured) region-of-interest (Yorke 2001, Troeller *et al* 2015). Data suggest that such NTCP models might fail to discriminate even at the level of physical dose whether an individual proton plan is effectively ranked superior to a comparison photon plan (Chaikh *et al* 2018, Kobashi *et al* 2018).

In addition, non-local effects are complicating comparisons: for instance, parotid tissue is treated for dose-constraint purposes as having uniform RBE, and thus even tissue radiosensitivity across the organ. Irradiation of the rat parotids with a proton beam showed that tolerance of the parotids to irradiation of a focal subvolume 'shower' (van Luijk *et al* 2015) is reduced by a sub-tolerance dose administered to a larger, surrounding volume 'bath' (van Luijk *et al* 2009). There might even be fundamental differences in normal tissue toxicities between proton and photon radiation due to not only the differences in the distribution of dose, which could interact with varying sub-region sensitivity across a larger organ, but also due to not well understood variations in RBE for normal tissue toxicities.

The questions of photon-based outcome modeling and RBE need to be considered also for model-based trial concepts, where a threshold restricts the cohort to theoretically favorable subpopulations (see article on 'Model based selection'). Toxicities in head and neck cancer have been used as examples for model-based trial approaches in PT (Langendijk *et al* 2013) but photon-based NTCP models can be insufficient for individual patient plan selection (Blanchard *et al* 2016).

Advances to meet challenges

Research is ongoing into defining more relevant dosimetric parameters that go beyond mean doses or even DVHs. Voxel-based approaches aim at exploring local dose differences associated with radiation toxicities. A

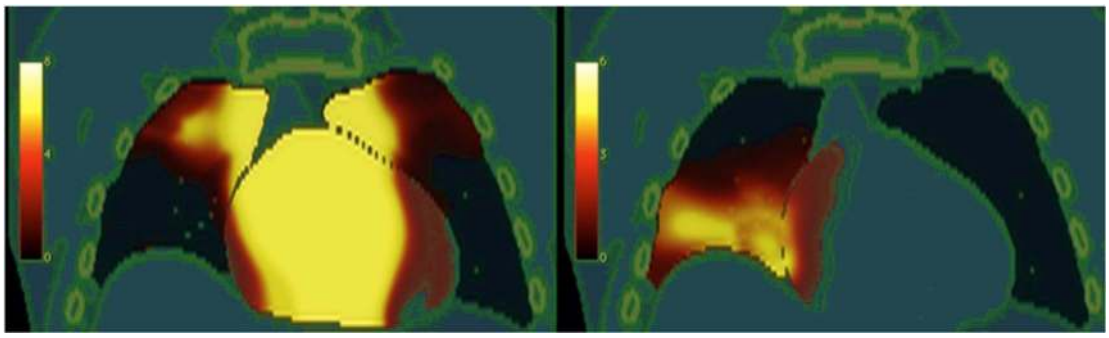

Figure 10. Left: significance map (–log *p*) of BED differences between IMRT and PSPT patients (spared regions), Right: significance map (–log *p*) of BED differences between patients who developed radiation pneumonitis and who did not (sensitive regions) (adapted from Palma *et al* 2019a, 2019b, © 2019 Elsevier Inc. All rights reserved).

voxel-based analysis of dose distributions can thus identify sensitive areas in organs independent from drawn contours (Han *et al* 2019, Palma *et al* 2019a, 2019b, Palma *et al* 2020, Monti *et al* 2020). Figure 10 shows an example illustrating where patients with radiation-induced lung damage received a significantly greater dose in parenchymal regions although overall low doses were delivered.

Refinements of outcome models based on these concepts benefit from data deduced from inhomogeneous dose distributions such as delivered in PT. This will lead to a better understanding of the mechanisms of normal tissue toxicities which will also improve conventional photon therapy. Furthermore, this will increase our understanding for which patient cohorts and treatment sites the advanced dose shaping capabilities of protons can be utilized towards a true outcome benefit.

While these approaches will improve our understanding of toxicities, outcome models relying on dose alone are unlikely to effectively predict toxicities (Rancati *et al* 2011). In addition to dose distributions, the use of blood and imaging biomarkers to quantify radiation injuries can be incorporated to inform predictive models, e.g. by leveraging deep learning methods to incorporate biomarkers and other confounding factors into a voxel-based dosimetric analysis. To consider the multidimensional nature of NTCP predictions, multivariable logistic regression modeling frameworks have combined dose-volume metrices with other patient- or disease-based prognostic factors using data-driven modeling to improve outcome prediction (El Naqa *et al* 2006, Lee *et al* 2014, El Naqa *et al* 2017). Risk factors can be included directly as features in data-driven approaches (Ibragimov *et al* 2019, 2020). Such approaches are likely more promising than efforts to base outcome modeling on mechanistic input parameters (Rutkowska *et al* 2010).

Concluding remarks

This article did focus on NTCP because this might be more relevant and specific to PT as long as prescription doses in PT are identical to those in photon therapy (except for RBE correction). However, moving forward, both hypofractionation and re-irradiation will increasingly being used in PT. This will cause proton specific aspects of TCP modeling to become more important. Note also that with re-irradiation becoming more common (a treatment where lower integral dose is particularly important), NTCP models need to be extended to scenarios in which multiple targets receive dose, or normal tissues are re-irradiated due to new lesions in the same organ.

Outcome modeling approaches for normal tissue toxicities can be divided into three classes (and combinations of them). One is mechanistic effect modeling, which is currently not feasible with clinically relevant accuracy. The second type are phenomenological analytical models based on clinical data, which are currently standard for most studies. These have now evolved by incorporating confounding factors and imaging biomarkers. The third approach are machine learning concepts which will play a bigger role to either complement our current outcome formalisms or even replace them altogether. Voxel-based dosimetric analysis as well as the incorporation of biomarkers will make this transition likely. These efforts will of course impact both photon and proton outcome modeling. However, PT will play a large role in research towards novel modeling approaches as the more inhomogeneous dose distributions and their variety will be advantageous for refining outcome models based on a better understanding of intra-organ sensitivity.

The aim will not be to develop proton-specific NTCP models but to challenge the current NTCP modeling concepts that are mainly based on two-dimensional dosimetric parameters and pre-defined structures and volumes of interest.

17. Biomarkers in PT

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Status

Technological advancements in radiation therapy have improved our ability to target and eradicate gross disease. We have also gained an increased appreciation for the potential side effects of radiation therapy, quantified the magnitude of such effects, and documented their negative influence on quality of life for cancer survivors. However, our ability to predict whether tumors will respond to treatment or patients will suffer from treatment-induced toxic effects is limited largely to classical dose-response relationships, and little is known about the susceptibility of individual patients and their tumors.

Efforts to improve tumor control have included various dose escalation or fractionation strategies, as well as sequential or concurrent treatment with chemotherapies or other antineoplastic agents. Such strategies have been successful in increasing tumor control rates, albeit at the cost of additional toxicity; however, we remain unable to predict either tumor response or radiation-induced toxic effects for individual patients. In part, this is because technological advances in radiation delivery have been driven by anatomic targeting based solely on physical factors. However, the intrinsic physical properties of how radiation interacts with cells and tumor tissue set a theoretical limit on the anatomic targeting of radiation. Currently, we know that radiation response is affected by various biological factors including genomics (Scott *et al* 2017), the microbiome (Reis Ferreira *et al* 2019) of tumor and normal tissues, the immune system (Twyman-Saint Victor *et al* 2015), and the tumor microenvironment (Vaupel 2004). Finding predictive features within these biological factors will add another dimension for predicting response or toxicity.

The term 'biomarker' refers to a measurable and quantifiable indicator of response. It stands to reason that maximizing cure rates and reducing toxicity will require biomarkers based on unique biological factors to predict tumor response or treatment-induced toxicity for individual patients, whether treatment is with radiation alone or in combination with molecularly targeted therapies.

An example of the need for biomarkers is highlighted by PT, a prime example of physics-driven technological advancement in radiation oncology for which biomarkers have not been explored. PT is expensive, and clinical evidence indicating its superiority to modern photon therapy is lacking. Therefore, biomarker development is crucial to facilitate the selection of appropriate patients for PT and thereby provide high-level clinical evidence supporting its use.

Current and future challenges

Most biomarker studies related to radiation therapy have focused on identifying predictors of tumor response to photon-based therapies (Yard *et al* 2016, Scott *et al* 2017, Manem *et al* 2019). Such predictive knowledge would allow stratification of patients into discrete groups based on likely response, and would allow treatment intensification or de-intensification or even prospective customization of dose and fractionation for individual patients. Although the potential for biomarkers is great, our understanding of factors associated with radiation response, even for photons, is limited. However, examples are emerging. A prime example of a potentially clinically useful predictive biomarker includes the human papillomavirus (HPV) status for patients with head and neck cancers. HPV-associated tumors have relatively high cure rates (Ang *et al* 2010), and dose de-escalation strategies that lead to less radiation-induced toxicity are now being assessed. Other attempts made to predict radiation sensitivity include assessing the clonogenic survival or DNA damage response of tumor cells cultured from individual patients. However, these approaches are labor-intensive and time-prohibitive for enabling rapid changes to clinical care plans.

Genomic techniques may hold more promise for this purpose (Yard *et al* 2016, Scott *et al* 2017, Manem *et al* 2019). Genomic biomarkers use genomic features of tumor or normal tissue samples in an attempt to identify patterns indicative of tumor response to radiation or radiation-induced toxicity. Tools to identify signatures of response are evolving rapidly and include newer bioinformatics techniques as well as the analysis of new publicly available datasets (Yard *et al* 2016, Scott *et al* 2017, Manem *et al* 2019).

In addition to blood or genomic biomarkers, imaging biomarkers may also be of great utility (Elhalawani *et al* 2018). Imaging in radiation oncology has historically been used for target delineation, verification of positioning, and response assessment. However, functional imaging modalities such as MRI may also provide insight into the biology of how tumors (or subsections of tumors) and normal tissues of individual patients

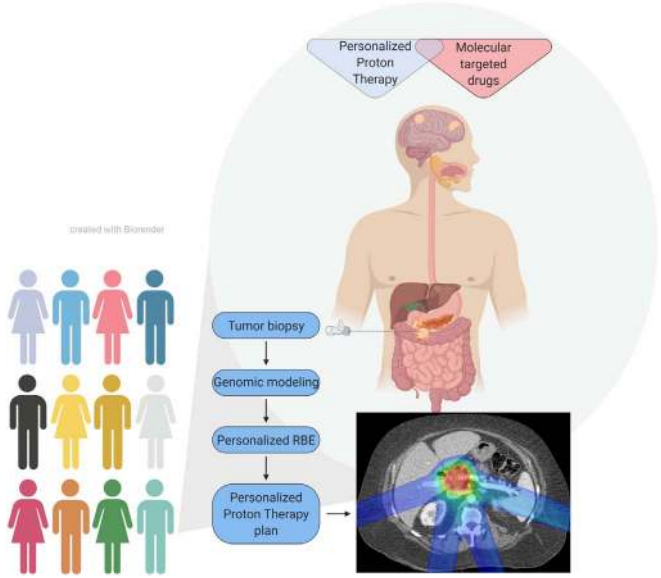

Figure 11. Illustration of a genomic biomarker framework to predict tumor response to proton therapy.

respond to radiation, which may relate to intrinsic radiation sensitivity. Like genomic biomarkers, imaging biomarkers may allow identification of patients who might benefit from dose escalation, thereby improving local control.

With respect to PT, for practical purposes the biological effects of protons and photons have been assumed to be relatively similar, with protons on average being 10% more biologically effective than photons; thus, a relative biological effect (RBE) value of 1.1 is used to normalize physical dose for treatments (see article on 'RBE'). However, at the cellular level, the patterns of proton-induced DNA damage differ from those of photons, particularly in areas of high LET. In studies of cell lines, these differences correlate with decreased clonogenic survival, resulting in RBE values approaching 1.8, even in areas proximal to the Bragg peak. More importantly, different cancer cell lines of the same histologic type have a large range of RBE values (Liu *et al* 2015). These differences in response likely arise from intrinsic genomic differences, such as capacity to repair clustered DNA damage, that are more likely to be affected by protons (Bright *et al* 2019). While in most cases such alterations are likely limited to the tumor itself, individual patients with particular germline mutations, which also affect normal tissues, must be carefully identified to avoid adverse radiation-induced toxic effects that could be induced by protons because of their higher RBE. The identification and quantification of predictive biomarkers of tumor and normal tissue response to protons would allow practitioners to identify patients whose cancer would be best treated with protons (aside from favorable dose distributions alone) while reducing toxic effects (figure 11). Other tumors with certain forms of DNA repair defects may be equally sensitive to photons and protons, and therefore use of protons for such tumors would be based on protons' superior dose distribution. On the other hand, tumors that are radiation-resistant to photons might be better suited for treatment with heavier ions, in which the still-higher LET may overcome resistance. Genomic approaches seem the most plausible to achieve this goal.

Advances needed to meet challenges

The primary challenge for all biomarker development is the need for large patient or preclinical datasets, with accurate response data coupled with genomic or other relevant information (see article on 'Outcome Modeling'). Although some datasets are being developed for photon radiation (Yard *et al* 2016, Scott *et al* 2017, Manem *et al* 2019), very few are available for PT. Hence, a necessary step will be the development of preclinical and clinical datasets of patients treated with PT. From a preclinical perspective, cellular response data can be obtained, albeit at high cost. Clinical datasets will be even more challenging, given the limited number of clinical proton centers and the general lack of banked tumor samples for future study. Successful advancement of proton (or particle) therapy will require significant funding and collaboration between numerous investigators. As sample acquisition and annotation improve, so will data analysis techniques such as machine learning and AI, which may even reduce the number of data points required. Another urgent need is information for predicting normal tissue toxicity, even for photons. However, investigations of normal tissue toxicity face greater obstacles, as severe radiation toxicity events are thankfully relatively rare.

Concluding remarks

A perceived challenge for biomarker studies is the prospective analysis of candidate biomarkers. However, the advent of proton and particle therapy may eventually necessitate the use of predictive biomarkers for selecting patients who will derive meaningful benefit from these modalities. Predictive biomarkers are now being used in trials of new anticancer pharmaceutical agents to select patients who will respond to those agents, which essentially biases such studies in favor of a successful trial. Future biomarkers may allow us to predict tumor and normal tissue responses that in turn may indicate an increased biological response to particle therapy, including protons. This, along with refinement of delivery technologies, would allow PT to reach its full potential in smaller, more efficient trials.

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18. Systemic effects of PT

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Status

The lower integral dose and reduced toxicity of PT offers an opportunity to explore clinical trials combining PT with intensified systemic therapy and/or dose-escalated radiotherapy. Proton chemo-radiotherapy administered concurrently has been shown to be associated with significantly reduced acute adverse events that caused unplanned hospitalizations, with similar disease-free and overall survival (Baumann *et al* 2019). While radiation therapy has mostly been combined with surgery and/or chemotherapy up to now, the cancer treatment landscape has changed significantly with the addition of targeted agents as well as immune-modulating therapies in recent years. Thus, even though combinations of radiation and drugs are the standard of care, the field is advancing quickly as new drugs and trial results become available. The combination of radiation with biological agents can have tumor-directed as well as toxicity-related effects, and interactions can be additive, supra-additive, or infra-additive. There is a paucity of clinical data regarding differences in proton versus photon outcomes in the setting of targeted therapy. However, there is emerging data that differences in signaling pathways with PT may help to overcome radioresistance (Konings *et al* 2020).

For instance, radiation therapy has both immune-stimulatory and immune-suppressive effects. The interaction of radiation with the immune system is complex and often difficult to interpret as radiation has detrimental effects not only on tumor infiltrating lymphocytes, lymphatic vessels and nodes, but also on circulating lymphocytes in the blood (Kaur and Asea 2012). In addition to baseline lymphopenia and other markers of inflammatory status in solid tumor patients, radiation-induced lymphopenia (RIL) develops in up to ~70% of radiation therapy patients (Yovino *et al* 2013, Wild *et al* 2016, Ellsworth 2018). In some photon radiation techniques (such as VMAT), large volumes of tissue receive low and intermediate radiation doses, which have shown to impact the circulating lymphocyte population (Tang *et al* 2014). High-grade RIL has been widely associated with poor overall survival, disease recurrence, occurrence of distant metastases, and reduced pathologic complete response rates in a variety of tumors (Grassberger *et al* 2019).

PT differs from photon therapies in the distribution of the low dose bath to the body outside of the planned treatment volume and also in the treatment delivery time within a fraction. Figure 12(a) highlights the dosimetric differences for an intracranial tumor treated with either photon and PT, which causes differences in dose to circulating lymphocytes (Fang *et al* 2018, Ko *et al* 2018). In studies on esophageal cancer it has been shown that patients treated with PT have a >50% lower probability of developing grade 4 RIL compared to patients treated with IMRT (Routman *et al* 2019), an endpoint correlated to overall survival (Davuluri *et al* 2017). Due to the lower integral dose, patients treated with protons had ~70% less grade 4 RIL compared to IMRT. However, this does depend both on target location relative to major vessels as well as differences in integral dose, and was not observed in a study of 150 patients with oropharyngeal cancer (Jensen *et al* 2017).

In addition to the radiation therapy modality, fractionation also affects the dose to the blood and the lymphocytes, thus possibly impacting outcome (Plowman 1983, Crocenzi *et al* 2016, Ko *et al* 2018). Lymphocyte sparing radiation therapy was suggested because stereotactic body radiation therapy resulted in significantly less RIL in pancreatic cancer (Wild *et al* 2016) and liver cancer (Gustafson *et al* 2017). Smaller target volumes and hypofractionated regimens may be associated with higher post-treatment lymphocyte counts. It has been estimated that during a conventional 30-fraction treatment with 2 Gy/fraction to an 8 cm diameter PTV, 95% of circulating blood receives >0.5 Gy with a mean dose to circulating blood of >2 Gy (Wild *et al* 2016) (figure 13). Field size and dose rate effects on lymphopenia for solid tumors have been explicitly studied (Ellsworth 2018). Not only dose to circulating lymphocytes but also dose received by tumor infiltrating lymphocytes, bone marrow, the lymphatic system and other lymphocyte reservoirs need to be considered.

In addition to radiation therapy impacting immune response, it also interacts with immune therapies. As radiation therapy has both local and systemic effects on the immune system, the combination of radiation therapy with immunotherapy represents a potential tool to maximize immune response and thus the efficacy of immune therapies (Kalbasi *et al* 2013, Vatner *et al* 2014, Seyedin *et al* 2015, Salama *et al* 2016, Wang *et al* 2018).

Current and future challenges

Particularly in terms of tumor response, it is important to understand the interaction of protons with those drugs that target specific DNA damage or repair pathways. For instance, drugs can provide tumor cell selective radiosensitization to be combined with radiation therapy (Morgan and Lawrence 2015). As discussed in the section on 'RBE' the proton RBE depends on DNA repair pathways and as such also the interaction of protons

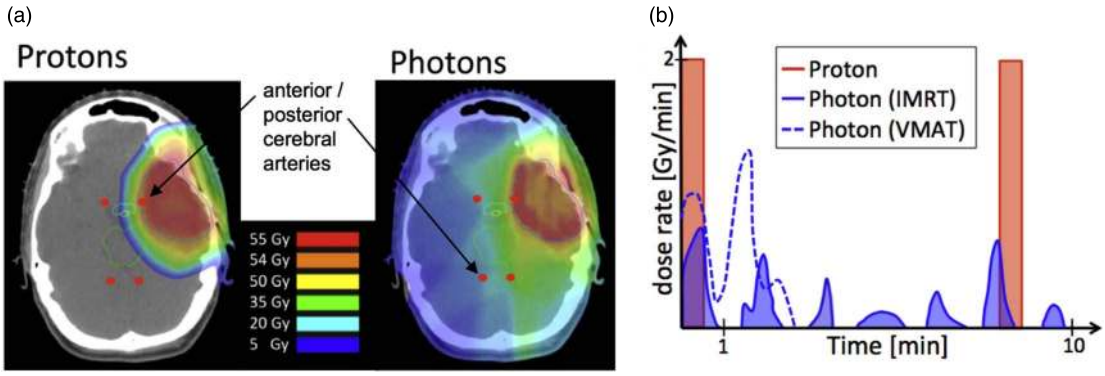

Figure 12. (a) left: Treatment plans for an intracranial tumor (left: IMRT; right: proton therapy). (b) Right: schematic illustration of the dose rate during a typical treatment for passively scattered proton therapy (red) and photon therapy (blue).

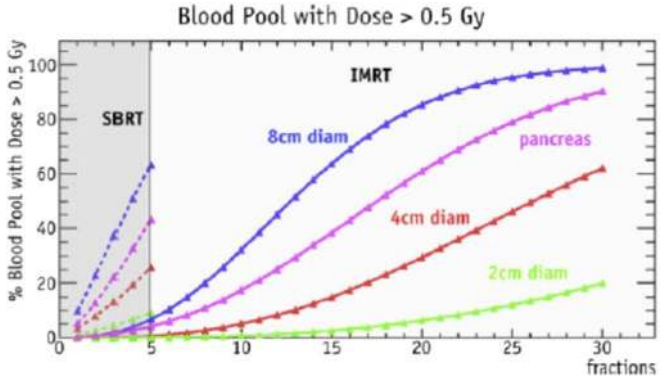

Figure 13. Lymphocyte sparing in pancreatic cancer using conformal treatments (Reprinted from Wild *et al* 2016, Copyright © 2016. Published by Elsevier Inc).

with drugs targeting DNA damage or repair can influence the RBE. Similarly, new agents that have overlapping toxicities with radiation have to be studied carefully to confirm the validity of toxicity response models, for example pneumonitis in the case of immune checkpoint inhibitors with thoracic radiation therapy (Hwang *et al* 2018).

In addition to standard cytotoxic agents, the efficacy of PT has to be analyzed in the context of immune therapies. Clinical data indicate that the low dose bath does affect the degree of RIL (Rudra *et al* 2018). On the other hand, it has been suggested that low dose whole-body irradiation might improve outcome after subsequent treatment regimens due to radiation induced antigen release (Liu *et al* 2010). In addition to dose-volume considerations, a faster rate of irradiation enables a larger fraction of circulating lymphocytes to be spared. The proportion of lymphocytes in circulation, and consequently at risk of being irradiated, might dictate the degree of systemic immune exposure. This is especially important for tumors that are close to major vessels, such as esophageal or centrally located lung cancers. Figure 12(b) illustrates dose rates to a voxel close to the target for a 7-field IMRT, a VMAT, and a passively scattered PT plan. Intensity modulated PT with its high degrees of freedom might offer new approaches to treatment optimization in the context of immune response or immunotherapies.

To better understand the effect of the radiation dose bath on the immune system, we need more data on the presumably high relative radiosensitivity of lymphocytes in terms of cell kill and functional inactivation (Radojcic and Crompton 2001, Vandevoorde *et al* 2016). The impact of radiation not only on circulating lymphocytes but also on lymphatic vessels, tumor infiltrating lymphocytes and immune-related signaling by normal tissues around the tumor needs to be better understood. Furthermore, predictive models of lymphocyte depletion rates and lymphocyte nadir as a function of dose distributions are needed to design clinical trials aiming at the optimal sequencing, prescribed dose, and fractionation of radiation with immunotherapy (Gunderson and Young 2018, Ko *et al* 2018). The role of PT in this context is extensively being studied (Ebner *et al* 2017, Fang *et al* 2018, Lee *et al* 2018, Tsuboi 2018).

The design of these clinical trials is challenging because of numerous potential combinations of systematic therapies, targeted therapies, immunotherapies, and radiation therapies. Furthermore, optimal combinations

might depend on baseline patient characteristics, meaning that different immune landscapes might require different therapeutic approaches to achieve the highest probability of immune activation. Testing all potential arms in clinical trials is nearly impossible so that bio-mathematical modeling is becoming more important to guide clinical trial design (Enderling *et al* 2019).

Advances in science and technology to meet challenges

Precision medicine in radiation oncology aims at defining parameters to identify patients that will benefit in terms of tumor control or normal tissue toxicities from specific modalities, e.g. cancer cells harboring certain defects in the DNA damage response are susceptible to PT (see secton on 'Biomarkers'). Mechanisms have to be analyzed also in the context of multi-modality therapies.

Understanding the potential biological and immunological differences of PT compared to photon therapy will reshape our understanding regarding the use of radiation therapy in general and PT in particular. Based on immune response data from patients on clinical trials, we might develop novel plan optimization strategies to mitigate adverse immune-modulatory effects of radiation therapy. This requires assessment of patient specific immune response during and after RT, either via circulating biomarkers or advanced imaging techniques (Grassberger *et al* 2019). This might ultimately lead to the establishment of personalized dose-volume constraints for immune structures and their inclusion in plan optimization. In this context PT will have significant impact due to its dose-shaping capabilities combined with a low integral dose. These constraints and predictive models will also allow for identification of patients at high risk of severe RIL who may benefit from PT. Especially when used together with drugs modulating the patient's immune response, a new planning paradigm might be required that takes the immune status of the patient into account, and ultimately treats the patient's lymphocyte reserve as a radiosensitive OAR requiring accurate dose calculation.

Concluding remarks

PT does interact differently with systemic therapies compared to photon therapies due to the reduced integral dose. In cases where radiation and systemic drugs target similar damage or repair pathways treatment plans may have to be optimized for combined modality treatments considering interaction terms. One prime example is the lymphocyte depletion due to the dose bath outside of the target. We are just beginning to understand the impact of radiation therapy on the immune system and the potential of radiation therapy in combination with immune therapies. Additional research is needed to assess if PT leads to enhanced systemic preservation of antitumor immunity or whether a low dose bath might even help to trigger immune responses under certain circumstances. Enhancing not only our physical and biological but also our immunological understanding of PT is critical to guide patient selection and to enhance the clinical effectiveness of PT in combination with checkpoint inhibitors and other approaches that interact with the immune system.

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