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Empowering Intensity Modulated Proton Therapy through Physics and Technology – An Overview

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Abstract

Considering the clinical potential of protons attributable to their physical characteristics, interest in proton therapy has increased greatly in this century as has the number of proton therapy installations. Until recently, passively scattered proton therapy (PSPT) was used almost entirely. Notably, overall clinical results to date have not shown convincing benefit protons over photons. A rapid transition is now occurring with the implementation of the most advanced form of proton therapy, the intensity-modulated proton therapy (IMPT). IMPT is superior to PSPT and IMRT dosimetrically. However, numerous limitations exist in the present IMPT methods. In particular, compared to IMRT, IMPT is highly vulnerable to various uncertainties.

In this overview we identify three major areas of current limitations of IMPT: treatment planning, treatment delivery, and motion management, and discuss current and future efforts for improvement. For treatment planning, we need to reduce uncertainties in proton range and in computed dose distributions, improve robust planning and optimization, enhance adaptive treatment planning and delivery, and consider how to exploit the variability in the relative biological effectiveness (RBE) of protons for clinical benefit.

The quality of proton therapy also depends on the characteristics of the IMPT delivery systems and image-guidance. Efforts are needed to optimize the beamlet spot size for both improved dose conformality and faster delivery. For the latter, faster energy switching time and increased dose-rate are also needed.

Real-time in-room volumetric imaging for guiding IMPT is in its early stages with CBCT and CT-on-rails, and continued improvements are anticipated. In addition, imaging of the proton beams themselves using, for instance, prompt gamma emissions, is being developed to determine the proton range and to reduce range uncertainty.

With the realization of the advances described above, we posit that IMPT, thus empowered, will lead to substantially improved clinical results.

1. Introduction

There is growing interest in and enthusiasm for using proton therapy (PT) in cancer management, as evidenced, in part, by the special issue in 2016 on particle therapy in the *International Journal of Radiation Oncology, Biology, Physics* [1] and the large number of publications on this topic cited in the book entitled *Principles and Practice of Proton Beam Therapy* [2] and in other books and articles [3]. According to the Particle Therapy Co-Operative Group (PTCOG), the number of proton therapy centers has increased by 40% within the last three years [4]. Presumably, this is due to the energy deposition characteristics of protons, which can provide clinically favorable dose distributions relative to photons, including considerable reduction in integral dose. However, accumulating clinical data have not yet provided an unequivocal demonstration of the increased effectiveness of PT compared to photon radiotherapy [5–8]. This lack may, in part, be due to the physical and technological factors that have prevented the realization of the true potential of PT. Up to now, the vast majority of proton patients have been treated with passively scattered proton therapy (PSPT) with its inherent limitation to tailor dose distributions, especially on the proximal side of the target. Another concern regarding PSPT is neutron dose, which is significant enough to pose an increased risk of secondary cancer among survivors [9–11], though such risk is lower than for photons [12, 13]. In addition, there are many limitations and uncertainties in PT as practiced today that have yet to be adequately addressed.

The most advanced form of PT, i.e., intensity modulated PT (IMPT), has become generally available only within the last five years or so [14–16]. IMPT, which uses pencil beam (or “beamlet”) scanning technology, provides dose modulation to optimally balance dose distributions to the target and various organs at risk (OAR). The term IMPT is generally used in place of a more precise term, 3D IMPT, which emphasizes that the modulation of combined dose distributions from all beams can be performed in three dimensions. In contrast, in intensity modulated x-ray radiotherapy (IMRT), intensity modulation in each beam is achieved in only two dimensions. In IMPT, intensities of beamlets for a sequence of proton energies from each of a set of beams are optimized simultaneously.

As the number of centers using IMPT increases, research and development efforts are concomitantly increasing to gradually overcome many of the limitations and uncertainties of PT as practiced currently. Referring to IMPT, Lomax [17] commented in 2015 that “PBS (pencil-beam-scanning) proton therapy and treatment planning is very much in its infancy.” We surmise that there will be significant improvement in the technological and physical aspects of IMPT in the next decade or two, which will substantially enhance the benefits of PT. The present status of PT can be likened to that of photon therapy prior to the development, introduction and evolution of IMRT and image-guided radiation therapy (IGRT) during the last three decades. The aim of this article is to discuss the current

limitations of and uncertainties in IMPT and describe on-going and future developments that will mitigate them, providing an unsurpassed treatment modality to improve outcomes.

In the following sections we discuss three major areas of IMPT relevance: treatment planning, treatment delivery, and motion management. Treatment planning subtopics include uncertainties in proton range and dose computations, robust planning and robust optimization, adaptive treatment planning and delivery, and relative biological effectiveness (RBE) considerations for protons. Treatment-delivery subtopics include improvement in proton beam characteristics, in-room image-guidance, contour-based beamlet scanning and proton range determination during treatment delivery. Various issues related to the impact of inter-fractional (e.g., tumor shrinkage, weight loss) and intra-fractional (e.g., respiration-induced motion) anatomy variations and strategies to mitigate their impact are also discussed. We assert that improvements in the technological and physical aspects of IMPT will further significantly enhance clinical outcomes and establish proton therapy as a standard treatment method for many types of solid tumors.

2. Physics and Biological Effectiveness Related Challenges in IMPT Planning and Potential Solutions

2.1 Range Uncertainty

A much discussed uncertainty in IMPT dose calculations is the range uncertainty (RU) of protons. RU compromises target dose conformality and homogeneity and increases the risk of over-dosing organs at risk (OARs) adjacent to the target volume. For over three decades, most proton centers have been using an RU of 2.5–3.5% of depth of penetration, plus an additional 1–3 mm for delivery system, biological and geometrical uncertainties. For PSPT, this would translates into a clinical target volume (CTV) expansion of, for instance, ~8 mm distally and proximally at 20 cm depth [18]. Below, we consider the factors contributing to RU and discuss approaches to minimize it.

Unlike dose calculations for photon radiotherapy, which employ electron density ratios (EDRs) that are related directly to the Hounsfield unit (HU) values derived from CT scans, dose calculations for proton therapy employ stopping power ratios (SPRs), whose relationship with HU's is more complex and is expressed through the Bethe-Bloch equation [19–21]. The current approach to SPR calculations is based on the stoichiometric technique pioneered by Schneider et al [22] and subsequently extended for Monte Carlo calculations [23]. It employs a parameterized model for the CT x-ray interaction cross-sections in tissues, which separates the dependence into CT-scanner and tissue composition terms, yielding a "virtual"-calibration-curve for HU to SPR conversion for human tissues. One fundamental shortcoming of the stoichiometric method is the degeneracy in the HU-to-stopping power calibration curve, i.e. materials with the same SPR can have different HU values. Also, the stoichiometric technique provides no information about the mean excitation energy of tissues (I_m), which is required by the Bethe-Bloch equation. Yang et al [24] performed a comprehensive analysis of proton RUs derived based on stoichiometric calibration and concluded that the final, combined uncertainty (95th percentile) for different treatment sites was 3–3.4%.

Paganetti [18] has analyzed various factors affecting RU and has indicated that uncertainties in the excitation energies of water (I_w) and tissues (I_m) contribute ~1.5% to RU, i.e. about half of the overall RU. The I value of water is often derived from direct measurement of proton range in water. However, as stated by Besmer et al, “even the determination of I-value of liquid water is not a trivial task” with associated uncertainties [25]. The aggregate results from the most recently published measurements suggest an I_w value of 80±2 eV, but the current NIST and ICRP value is 75 eV [25]. A consensus is needed on the accepted I_w value and the associated uncertainty.

The discussion of the I value of tissues is more complicated [3]. Planning systems are commissioned using measurements in water and range uncertainties in tissues are not absolute but derived from measurements in water. Schaffner et al [26] experimentally verified the stoichiometric method and showed that SPRs can be determined with an accuracy of 1.1% and 1.8% for soft tissues and bone, respectively. However, it should be noted that the SPRs were for individual homogenous tissues from animals, and all measurements were performed under ideal experimental conditions. Thus, the direct applicability of their results to clinical PT may be questionable.

Although the stoichiometric method has led to a significant RU improvement, there are other techniques that may further improve SPR accuracy, for instance the use of dual energy CT (DECT). Conventional CT does not provide adequate data for accurate SPR determination. More appropriate data include the effective atomic number (Z_{eff}) and the I value of the heterogeneous human tissues. This has led to studies using DECTs, which perform scans using two different kVp x-ray beams, e.g. 80 and 120 kVp. Yang et al [27], in a theoretical study, demonstrated the feasibility of using kVp DECT to determine Z_{eff} in addition to the electron density ratio. Importantly, they also showed that I_m values can be derived from Z_{eff}. This additional information improves the accuracy of the proton stopping power calculation using the Bethe-Bloch equation. In their follow-up theoretical work, Yang et al [28] reported that DECT combining MV and kV images yielded even better accuracy and predicted a roughly 50% reduction in RU compared to the stoichiometric method using conventional CT. More recently, a University of Heidelberg group performed an experimental study using a commercially available DECT scanner, the Siemens’ Somatom Definition Flash [29, 30]. First, I-values were parameterized as a function of Z_{eff} for 71 tissues described in ICRU-49 [31] using I values of individual constituents and Bragg’s additivity rule. An equation was then derived for SPR calculation using DECT data. For experimental verification of their method, they scanned 20 tissue surrogates with DECT to determine their EDRs and Z_{eff} values and calculated their SPRs. They then measured the SPRs of the 20 materials using a carbon beam and found the agreement to be within 0.6% for tissue surrogates.

Various centers, including Heidelberg, MD Anderson, and the University of Maryland, have installed DECTs and are investigating their application to reduce RU in proton dose calculations. This approach is clearly low-hanging fruit to improve IMPT. It is also worth noting that proton radiography is being investigated for the determination of proton stopping powers.

2.2 Computation of Dose Distributions and Related Quantities

One of the important sources of uncertainties with a potential to affect the efficacy of IMPT is the approximations in methods used for dose computations in the current treatment planning systems. Potential impact uncertainties in dose computation has been documented in the literature [32, 33]. Improvements in this area can be achieved with a relatively modest effort.

Dose distributions, computed using CT data, are the bases for the planning of treatments. The accuracy of computed dose distributions depends on a number of factors. These include the random and systematic uncertainties in CT numbers, the factors to convert CT numbers into stopping powers ratios (SPRs) as discussed in section 2.1, and the assumptions and approximations in the semi-empirical formalisms and algorithms for dose computations. Moreover, the inability of the imaging systems to accurately image high-Z materials, such as dental fillings, may introduce large errors in CT numbers and produce artifacts that obscure tissue boundaries. Uncertainties related to CT numbers and imaging artifacts have a more pronounced impact for protons than for photons. DECT scanners can not only greatly reduce many of the systematic errors but can also reduce high-Z artifacts compared to those in images from conventional single energy CT (SECT) scanners.

For practical reasons, for instance to achieve adequate speed for the planning of treatments on affordable computers, analytic semi-empirical models of proton dose computations make numerous assumptions and approximations. Examples include the use of ray tracing to correct for tissue heterogeneities, the assumption of slab geometry when estimating the lateral spreading of proton beamlets passing through heterogeneous media, the neglect of scattering from apertures (or MLCs), the assumption that the nuclear component of beams can be accounted for by a simple offset at the end of calculations using the approximate analytical algorithms, the neglect of scattering from beam line components such as a profile monitor, etc. Monte Carlo (MC) techniques, or their accelerated variants (accelerated Monte Carlo – AMC), are necessary to overcome the limitations of such approximations and assumptions. MC methods are also essential for calculating other physical quantities, such as linear energy transfer (LET), required for computing RBE.

Fortunately, several academic institutions and vendors are developing and investigating MC methods. These methods utilize statistical techniques to track a large number (typically millions) of protons and their secondary progeny to determine their dose deposition. The traversal of protons is tracked through the components of the delivery system as well as the patient anatomy represented by the CT image. Even with the fastest affordable computers, MC methods are not as yet fast enough for proton dose calculations for routine practice. This is due, in part, to another dimension, i.e., that of a sequence of proton energies, which increases the CPU time requirements by more than an order of magnitude. Computational resource requirements can be many times greater still for such applications as 4D (incorporating respiratory motion) and 5D (incorporating 4D and inter-fractional variations) IMPT optimization, and for robustness evaluation, robust optimization and beam angle optimization.

To overcome the computation speed problem, accelerated MC methods (AMCs) are being developed that are essentially as accurate as the full-fledged MC but are two or more orders of magnitude faster. An example is the “track repeating algorithm” [34, 35] in which proton tracks and their interactions in water and other materials are tabulated after they have been simulated using standard full Monte Carlo. The changes in location, angle and energy for every step and the energy deposition along the track are recorded for all primary and secondary particles and re-used in subsequent AMC simulations. Such methods avoid complex physics processes in tracking particles and are, therefore, considerably more efficient with a minimal compromise in accuracy.

In addition to accelerating MC itself, the use of specialized hardware, such as graphical processing units (GPUs), can achieve considerable additional speed [36–38]. GPU implementations may require the introduction of some approximations for some applications due mainly to the memory limitations of currently available hardware.

In a typical MC or AMC process for the computation of dose and LET distributions, beamlet phase spaces (i.e., proton positions, directions and energies of a large number of particles) in a plane normal to the beamlet direction for a complete set of discrete energies is pre-computed. These phase spaces are used as a starting point for tracking particles in the patient (and through an aperture, if one is present) for IMPT dose calculations. The use of AMC systems and specialized hardware can contribute significantly to the enhancement of the state of the art of IMPT.

2.3 Robustness Evaluation, Robust Planning and Robust Optimization

For IMRT, the dose distribution may be described as a “dose cloud” in space, which is perturbed minimally with small changes in patient position or anatomy. In contrast, IMPT dose distributions may be significantly altered by small changes, potentially causing undesirable consequences for both target coverage and OAR sparing. Many of the IMRT planning techniques, developed over the last few decades, are not extensible to proton therapy since special strategies are needed to incorporate the various uncertainties into the planning and optimization of IMPT so that the resulting dose distributions are robust. Indeed, several robust IMPT methods have been developed, which, we expect, will continue to be improved over time.

2.3.1 IMPT plan robustness evaluation—Among the low hanging fruits to enhance the utility of IMPT is the evaluation of robustness of IMPT dose distributions. For IMPT, the dose distributions due to individual fields tend to be highly complex and have high gradients, which, when combined, ‘fit’ something like a jigsaw puzzle to produce the desired pattern of homogeneous dose distribution in the target and adequately spare OARs. However, in the face of uncertainties, the ‘fit’ is lost, creating hot and cold regions. The goal of robustness evaluation is to assess the resilience of a dose distribution to uncertainties as a part of the assessment of a treatment plan. A simple strategy being introduced currently is to compute dose distributions for each of a sufficiently large set of uncertainty scenarios and plot a family of DVHs for each anatomic structure of interest. The band of DVHs for a given structure represents the range of possible dose distributions. A narrow band means high

robustness and vice versa. In analogy with the photon domain, where the DVH of the PTV is the "worst case" representation of the DVH of the CTV, for proton treatment planning one may select the CTV DVH that corresponds to the overall worst case scenario for robustness evaluation.

Bandwidth at critical dose-volume points on the DVHs (e.g., at D95 for CTV or V20 for lung) may be used as a quantitative measure of robustness. Other ways of quantifying robustness have also been proposed. For instance, one could compute the area of the DVH band as a robustness measure. Another approach, proposed by Liu, et al [39], is the root-mean-square dose-volume histogram (RMSD-VH) in which the dose spread in each voxel is represented by the root-mean-square of dose for a number of uncertainty scenarios. The area under the curve of the RMSD-VH may serve as a quantitative index of robustness. In addition to the use of DVHs, one can also calculate the spread of values of EUDs, TCPs and NTCPs, etc. and use the ones corresponding to the worst-case plan for the evaluation and inter-comparison of competing plans.

2.3.2 Robust planning and robust optimization of IMPT dose distributions—

There are several measures one can take to enhance the robustness of an IMPT plan. The use of a larger number of beams would reduce the impact of uncertainties, but at the cost of increased delivery time and the extra effort required for QA. These may be minimized through automation of delivery without re-entering the treatment room and by streamlining the QA processes. Another way of improving robustness is to avoid beams through complex heterogeneities if achievable without compromising optimality. The passage of beams through highly heterogeneous anatomy, e.g., through head and neck and lungs, increases uncertainty and leads to reduced robustness. Robustness is also affected by spot size and spot spacing, but there are tradeoffs. For instance, larger spot sizes would improve robustness but at the cost of achievable conformality.

The ideal method of improving robustness of IMPT dose distributions is with the aid of robust optimization methodology. Such optimization considers dose distributions for a sufficiently large number (9 to 30, or even more, have been reported) of uncertainty scenarios and optimizes them so as to optimally satisfy the specified criteria simultaneously under all scenarios. The uncertainty scenarios are typically selected from proton range uncertainty and setup variations along all directions. The impact of respiratory motion may also be incorporated.

In one such approach, called the "voxel-wise worst case" robust optimization [39, 40], the optimization algorithm computes the score (the value of the objective function to be minimized) in each iteration by selecting the worst dose in each voxel from among multiple scenarios. For the target volume, the worst case dose would be the minimum value in each voxel, and for each normal tissue, it would be the maximum value. Alternate worst-case approaches have been proposed and have different strengths. Fredrickson, et al, for example, have proposed the "minimax" worst-case approach in which the dose distribution corresponding to the worst score of the plan as a whole is selected in each step of the process of minimizing the objective function [41–43].

A fortuitous result of robust optimization that has been observed is that robust optimization may make dose distributions resilient not only to uncertainties that were included in the optimization process but also to some that were not explicitly considered. For instance, robust optimization that considers only setup and range uncertainties may lead to dose distributions that also have improved robustness in the face of inter- and intra-fractional anatomic variations. Apparently, robust optimization implicitly reduces the gradients in dose distribution per field as well as in the composite, which means that the dose distribution becomes less sensitive to variations in anatomy in general.

Robust optimization is an important tool to significantly improve the confidence in IMPT dose distributions and to improve their optimality. Considerable additional work is needed to improve our understanding of the currently implemented robust optimization methods, to develop new ones, and to extend these methods to uncertainties other than setup and range. Robust optimization methods are likely to be available in commercial IMPT planning systems in the not-so-distant future. It is worth pointing out that, although robust optimization is new to our field, it has been applied for decades in other fields, including statistics, operations research, finance, engineering, etc., wherever uncertainties play an important role.

2.4 Contour-Based IMPT Scanning

Currently, beamlet spots are placed on rectilinear grids with uniform spacing at each water-equivalent depth for IMPT delivery. To provide sufficient coverage of the target, this technique may necessitate placement of spots outside the target, leading to unnecessary dose to normal tissues. A remedy for this is contour-based spot placement as suggested and investigated by Meier et al [44]. In their study of several chordoma cases, they developed a method that allows flexible beam spot placements both along the contours of, and within, the target volumes. The contour-based method has been shown to reduce the OAR dose by up to 20% but at the cost of increased target dose heterogeneity.

In a further development, the PSI group has explored two approaches to contour-based scanning (private communication, Lomax 2016): concentric contour scanning and hybrid spot placement. In the first method, the target is modeled as a 3D wireframe, based on which concentric contours spaced ~4 mm apart are constructed in the planes perpendicular to the beam direction. Beam spots are then placed along the concentric contours. The concentric approach leads to dose inhomogeneity in the treated volume, which may be reduced by hybrid spot placement in which the contour-based and rectilinear approaches are combined. Planning studies and measurements show the promise and potential of such approaches in improving IMPT dose distributions.

2.5 Relative Biological Effectiveness and LET Issues in IMPT

In the current practice of proton therapy, the RBE of protons relative to photons is simplistically assumed to have a constant value of 1.1 for all situations. This assumption is based on averaged data from a number of historical experiments performed under limited conditions [45]. Increasingly, it is being recognized that RBE may vary substantially along the path of a proton beam. As a consequence, the biologically effective dose distributions

actually delivered may lead to suboptimal treatments and unforeseen local failures or toxicities [46, 47].

The need for improved understanding of proton RBE is amplified in IMPT since each of the IMPT beams has a highly heterogeneous dose distribution, which magnifies the effect of the complexities of RBE. Conversely, the inherent flexibility of IMPT offers an opportunity to capitalize on the high RBE around the Bragg peak through the incorporation of such information into IMPT optimization to produce more effective treatments.

In order to unequivocally demonstrate the advantage of IMPT, it is essential to understand the clinical effects of the variability of RBE on treatment response. To reveal the clinical consequences of RBE, it is important to mitigate other sources of uncertainties and to incorporate the residual uncertainties into computed dose distributions. The resulting knowledge could lead to the development of more reliable models of predicting RBE as a function of dose, LET, α and β values of the tissues. Current models, in general, are simplistic and typically lead to proton RBE that is a linear function of LET [48, 49], which is not consistent with the results of recent high precision experiments [50].

Reliable RBE models are essential not only for evaluating the potential clinical impact of IMPT dose distributions but also for optimizing IMPT dose distributions to maximize the biological effect (cell kill) within the tumor target. It is noteworthy that the main rationale for using protons is their characteristic Bragg curve. The fact that the RBE-weighted dose at the Bragg peak may be 30–40% higher than the entrance dose compared to the physical dose indicates that the use of variable RBE should, therefore, lead to an even greater differential between the tumor target (GTV or CTV) and the normal tissue biologically effective dose compared to the assumption of a constant RBE. One way to achieve this differential is to perform IMPT optimization based on criteria defined in terms of the RBE-weighted dose computed using a variable RBE model, an approach that is already being used for carbon therapy [51]. Even a simple variable RBE model could direct higher RBE protons into the target and away from normal tissues. An alternative strategy is to base the criteria on dose x LET to minimize LET in critical normal tissues [47]. There are other strategies for maximizing the biological effect or for forcing the high LET protons into the target volume and away from normal tissues. Examples include constraints on LET, optimized placement of spots, etc. There is a need for considerable further research to fill large gaps in our knowledge of RBE. Such research should include analyzing clinical outcomes data incorporating RBE and LET information. There is also a need to further refine existing models or develop new ones for predicting RBE. Additional research and development is also necessary to inter-compare and determine the best approach to incorporate the biological effect models for the evaluation of computed biologically effective dose distributions and for the optimization of IMPT. Finally, it is necessary to evaluate the impact of such factors as inter- and intra-fractional anatomy variations on biological consequences and in regions affected by distal edge degradation. Such research is critical to exploit and demonstrate the true potential of IMPT.

2.6 Adaptive Planning and Treatment

As stated previously, IMPT dose distribution is highly sensitive to changes in patient anatomy. A number of studies have reported the necessity of adaptive planning for proton therapy, as even small variations in anatomy may lead to significant changes in dose distribution [52, 53]. Prior to the availability of in-room CT or CBCT, adaptive planning had to be performed offline. With the recent availability of such devices, the re-planning workflow is undergoing evolution.

2.6.1 Adaptive planning process—Although CBCT has been available for more than 15 years for IMRT, similar capabilities have been becoming available only recently for IMPT. CBCT is essential for assessing set-up accuracy prior to each treatment session and for monitoring inter-fractional anatomical changes. Such changes could serve as a "triggering event" for adaptive re-planning.

In-room CT-on-rails is an alternative to CBCT, preferred by some because of its better image quality, but it has the disadvantage that the patient is not in the actual treatment position. For adaptive treatment, it does have the advantage of providing more accurate CT data for dose calculations for re-planning. There are current developments to improve the image quality of CBCT; only time will tell if the improved CBCT images can rival those of the CT-on-rails. Moreover, CBCT does not have sufficient cephalad-caudad coverage, though here have been recent studies on the use of "synthetic" CT, in which deformable registration is used to map the Hounsfield units from the simulation CT onto the CBCT to provide the missing anatomical information [54].

A new CT image (often called the "verification image") may be acquired frequently, e.g., on a weekly basis. If a significant difference is found to exist between the reference (planning) and verification images, the dose distribution may be re-computed with the current beam arrangement applied to the new CT image. If the new dose distribution fails to meet the original criteria for target coverage or sparing of critical normal tissues (the "triggering event"), the plan should be re-optimized. Ideally, re-optimization should consider the dose distribution already delivered, which would require deformable registration to map the dose distribution delivered to date to the new image. Similarly, at the end of the course of treatments, cumulative dose distribution may be computed, which would also require deformable registration techniques. Delivery of adaptive treatment is more practical with IMPT relative to PSPT as physical collimators and compensators are not needed.

2.6.2 Should the doses from the adaptive plans be summed?—There is some controversy regarding whether to deform dose distributions using deformable image registration (DIR) for adaptive radiotherapy for photons [55] and to accumulate them onto a reference image. Some believe that unless one can firmly establish that a voxel after DIR contains the same biological tissue as the original voxel, it would be inappropriate to sum the dose. The accuracy of cumulative dose to the tumor may be highly questionable due to the changing shape of the tumor. On the other hand, cumulative dose to normal tissues that do not deform significantly may be adequately accurate.

3. Treatment Delivery Related Challenges and Potential Solutions

It is important to improve the characteristics of the scanning proton beamlets as they influence achievable dose distribution and the efficiency of the clinical workflow for IMPT delivery. Examples include beam spot size, penumbra, dose rate and beam energy-switching time. As these characteristics are generally machine specific and inter-connected, only a general discussion is possible.

3.1 Beamlet Spot Size

There has been considerable discussion in the literature on the scanning beam spot size. It governs the achievable penumbra and affects control over dose distributions. The increase in spot size near the end of the proton beam range is unavoidable due to multiple Coulomb scattering in the medium. It is intuitive that the smaller the spot size, the sharper the penumbra and more conformal the PT dose distribution. At present the in-air σ's of beamlets at the isocenter available in commercial systems can be as small as 3 – 4 mm at high energies and 5.5 – 6 mm at low energies (~70 MeV). Aside from the use of smaller spot sizes, another method for reducing the penumbra and achieving superior conformation is by optimizing the spot spacing and weights.

In a 2003 planning study for IMPT, Trofimov and Bortfeld [56] suggested that beamlets with 5 mm σ in air is sufficient for most clinical cases, a condition satisfied by some current commercial treatment delivery systems. On the other hand, recent studies on head and neck treatment and brain radiosurgery have demonstrated the benefit of further reduction in spot size in the sparing of normal tissues, e.g. salivary and parotid glands and normal brain [57, 58]. Thus, to achieve higher conformity, it is beneficial to generate beamlets of smaller σ, particularly for treatment sites with depths < 10–12 cm. Engineering efforts to reduce the spot size without compromising dose-rate is therefore a high priority [59]. Ironically, the spot size (in air) increases with decreasing proton energy, and the use of collimators in the beam line may be needed to sharpen the beam boundaries, which some vendors are planning to achieve with MLCs. However, the use of conventional MLCs for proton therapy is not pragmatic in most cases and has not been successful so far [60, 61]. This is, presumably, due to their large bulk and slow speed to adapt dynamically to changes in aperture to achieve three-dimensional conformation.

While a smaller spot size may yield more conformal dose distribution, a larger spot size produces more robust dose distribution. In some cases, a single spot size may suffice, but in other cases it may be desirable to have the flexibility of selectable spot sizes. For example, an ideal scenario would be to use a small spot-size for the target periphery for penumbra reduction and a large spot-size in the center for faster delivery and better robustness. To switch from one spot-size to another during the delivery of an IMPT field would be challenging. An alternative would be to deliver the first part of the treatment field with one spot-size, followed by a spot-size change, and the delivery of the remainder. A spot size switching time of, say, 10 seconds, may be clinically acceptable. Although significant engineering efforts would be needed to make selectable spot size possible, vendors are beginning to provide such an option.

3.2 Energy-Switching Time

An IMPT beam is delivered in multiple “layers”, one layer per energy. Currently, the energy-switching time of most commercial scanning beam delivery systems varies from slightly less than 1 second to over 2 seconds. PSI has reported a switching time ~0.1 seconds [62], demonstrating that engineering efforts can reduce the energy switching time in commercial systems significantly. Assuming a decrease from 1 second to 0.2 seconds, the reduction in time to deliver a typical IMPT beam may be ~0.5 minutes, and the entire treatment may take ~2 minutes, which is helpful but not truly significant. However, faster energy-switching times could facilitate dose repainting, useful for mitigating the “interplay effect” for targets affected by respiratory motion and for making respiratory-gated IMPT more efficient. The interplay effect is the occurrence of hot and cold spots in the dose distribution resulting from the asynchronous simultaneous motion of the tumor and the scanning beamlet. Energy-switching time is also dependent on the type of machine, e.g., cyclotron or synchrotron, which needs to be looked at carefully.

3.3 Dose Rate

Due to their respective underlying basic principles, the average beam intensity exiting a cyclotron is much higher than that of a synchrotron, with some cyclotrons capable of generating 800 nA. For a typical 2 Gy per fraction treatment, only 0.4 nA is needed from the nozzle; although 8 nA can be obtained, which would translate to a dose-rate of 40Gy/L/min. Current upper limits to dose rate are due to engineering and safety considerations. Higher dose rates would be highly desirable, especially for SRS and SBRT with IMPT.

Current IMPT delivery systems also constrain the minimum MUs per spot due to the limitations of the beam monitoring systems to detect the spot position and dose rate with acceptable accuracy. Such constraints require that the planning system eliminate spots with intensities below the threshold of detectability. This inevitably leads to the degradation of optimized dose distributions, but it may be partially offset with special re-optimization techniques. Nevertheless, there is need to reduce these constraints using novel detectors.

3.4 Collimation to improve conformality of IMPT dose distributions

Of the many suggestions to improve proton beam penumbra, the simplest is to add an aperture. IMPT, by its very nature, produces dose distributions that conform to the target volume in three dimensions. Thus the use of a single aperture (or an MLC to form a static aperture) would trim the penumbra only at the largest cross-section of the target volume perpendicular to the beam direction and does not provide protection to adjacent normal tissues at all depths. The use of MLC for proton therapy has been the subject of controversy as discussed in a point/counterpoint article in Medical Physics [63]. To date, the use of the dynamic or moving MLC mode to trim the beamlet penumbra has not been studied for IMPT.

Another approach to reduce IMPT penumbra, called the dynamic collimation system (DCS), has been suggested by Hyer et al [64] They have developed a prototype that employs moveable metal blades to intercept the scanning beam at the lateral edge of the tumor volume, thereby trimming the penumbra. A recent treatment planning evaluation of brain

and head and neck cancer patients indicated that the use of DCS improved target dose conformality [65]. The development of clinically useful DCS systems will involve a major engineering effort and further careful consideration of specifications with regard to the applicability of the DCS to different disease sites. In fact, given the inherently larger lateral spreading in tissues due to multiple coulomb scattering of higher energy protons for deep-seated tumors, Hyer et al [64] designed their DCS mainly for proton energies of < 150 MeV, thus reducing the thickness of the blades and the load on the mechanical drive mechanism.

For both MLC and DCS systems, consideration needs to be given to the radioactivity induced in the device components by the secondary neutrons [61] and to the trade-off between improved PT dose conformality and the increased neutron and activation dose to the patient and the healthcare providers.

4. In-room imaging and image-guidance for IMPT

Over the last two decades, in-room image-guidance for IMRT has gradually advanced and now includes MV portal imaging, MV CBCT, planar and stereotactic kV projection imaging and kV CBCT. However, until recently and despite the greater vulnerability of protons, especially of IMPT, to sources of uncertainties, the greater need for volumetric image guidance for IMPT was largely unmet. Only kV projection imaging was available. Fortunately, CBCT capabilities are now becoming commercially available on the new treatment delivery systems. In addition, some proton centers are using CT-on-rails. Different institutions are choosing different approaches in collaboration with proton machine and imaging systems vendors.

Because of uncertainty in the range protons and the sharp distal fall-off, real time imaging of proton beams is another important aspect of in-room imaging.

4.1 CBCT, CT-on-rails, and CBCT image improvement

As mentioned above, CBCT is important for set-up accuracy for IMPT, for monitoring inter-fraction anatomical changes, and to act as a “trigger” for adaptive re-planning. The use of in-room CT-on-rails as an alternative to CBCT is also an option. For both CBCT and CT-on-rails, imaging artifacts may be caused by organ motion. Moreover, while 4D imaging methods are now available, the appropriate use of motion-correlated images for treatment planning and guidance requires careful consideration for protons, especially for IMPT, due the possible interplay effect, which is more pronounced for IMPT than for IMRT.

Proton therapy gantries are often equipped with two or three kV imaging systems, which permit stereotactic imaging. In addition, there is the possibility of simultaneously using both kV imaging systems for CBCT data acquisition. If used at the same kVp, the dual imaging systems would provide faster CT data acquisition. If used at different kVp’s, one could explore the usefulness of dual energy CBCT, perhaps for improved anatomy visualization and as a substitute for DECT.

4.2 Proton Range Determination during IMPT Delivery

There is ongoing research to experimentally determine the position of the Bragg peak during IMPT delivery. Methods include both direct (implanted dosimeters) and indirect methods, e.g. prompt gamma, Compton camera and iono-acoustic imaging [66, 67]. For such measurements to be meaningful, the results need to be spatially correlated with patient anatomy in the treatment position.

Prompt gamma imaging is the detection of gamma rays emitted by the nuclei excited by interaction with protons and decaying to the ground state. The high correlation between the prompt gamma signal and the Bragg peak, together with the short time scale of the prompt gamma emission, make this a promising solution for real-time verification of proton dose delivery. There are a number of methods for imaging prompt gammas, the simplest being a row of thick scintillators behind either a knife-edge slit or a multi-parallel slit collimator [68] [69] [70]. Another promising technology is the Compton camera, which combines the information from both the time and spatial domains of detected gammas to deduce their source. This technique requires no collimation and has the potential to provide real-time 2D and 3D dose profiles and information on the Bragg peak position.

Yet another approach for range verification using prompt gammas is similar to the slit approach, but it employs fast scintillators for energy resolution and real-time gamma spectroscopy. Detection of changes in the spectroscopic profile along the beam path due to proton-nuclear interactions enables the determination of the position of the Bragg peak [71]. The spectroscopic information also provides details of the material composition, which may prove beneficial.[72]

Another novel approach is the so-called prompt gamma timing method, which entails measuring the difference in the time between the entry of the proton beam into the medium and its stopping at the Bragg peak [73–75]. Thus far, only experimental investigations have been conducted. The advantage of this technique is the small footprint of the device without the need for collimation. Its disadvantages are the requirement for accurate proton transit time measurement, which could be compromised by the time-width of proton bunches [74].

Many challenges remain in prompt gamma imaging, including low signal-to-noise ratio, expensive electronics, complex reconstruction algorithms, inability to use full treatment beam intensity due to detector saturation, etc. Moreover, all of the prompt gamma techniques share the problem of requiring careful registration of the camera/detector coordinates with the patient coordinates in order to know the position of the detected signal relative to the patient geometry. This registration is possible using pre-treatment CBCT and accurate indexing of the range-measurement-device to the CBCT coordinates. The clinical feasibility of prompt gamma imaging techniques continues to be explored [73].

Another range verification method worth mentioning is iono-acoustic imaging, which uses the acoustic waves generated by the proton pulses in the body to create an image of the positions of the Bragg peaks [76]. This technique is very much in the concept phase, with only calculations and a limited amount of experimental data showing its feasibility in

homogeneous phantoms. Heterogeneity and organ motion are expected to add significant complexity to acquire a meaningful image.

In theory, the best method to determine proton range and stopping power is by measurements using protons themselves. In this regard, there has been ongoing research on proton radiography and proton CT. To date, commercial proton delivery systems provide sufficient energy only for head and neck proton imaging. Even for head and neck, proton radiography as well as proton CT have poor image resolution due to multiple coulomb scattering; although the clinical feasibility of this technology is being actively explored [77]. Proton radiography and CT for other disease sites would require higher proton energies [78].

5. Respiratory Motion Management

Respiratory motion is challenging to manage in radiation therapy due to the irregularity of the breathing cycle time and amplitude and abrupt movements due to coughing, target drift, inter-fractional irreproducibility, etc. There is a large body of literature dealing with motion management in photon radiation therapy, some of which can be applied to proton therapy as well [79–88]. Bert and Durante [89] have provided a comprehensive report on the motion issues in particle therapy and suggested some solutions [90]. It is important to note that, for particle therapy, it is not just the motion of the tumor but motion of any tissues in the path of protons that can perturb the dose distribution pattern. Another issue of greater importance to proton therapy is the interplay effect, as discussed in section 5.1.3 below.

5.1 Respiratory Management for IMPT Delivery under Free Breathing

Motion management in radiation therapy using 4D images has been discussed in detail for photon therapy. The simplest widely practiced option for proton beams is to define ITV (internal target volume that encompasses the CTVs on all phases of respiratory cycle as derived from the 4D CT). An IMPT plan designed using the ITV is then delivered in free-breathing mode. An alternative IMPT free-breathing delivery approach is to design IMPT dose distribution using 4D robust optimization (Liu, et al and Ge, et al [91, 92]). In 4D robust optimization, the 3D robust optimization technique discussed above is extended to optimize IMPT dose distribution taking into consideration all respiratory phases. Another approach to the delivery of IMPT in free-breathing mode is to reduce target motion. A commonly used technique to reduce target motion in the photon domain employs an abdominal compression device. Respiration induced motion may also be reduced using supplemental oxygen. Such approaches are appropriate for protons as well. Clearly, the ITV (or free breathing) approaches, though more efficient in terms of delivery time, would perturb dose distributions when beams pass through heterogeneities and may lead to excessive dose to normal tissue and may also compromise target coverage.

5.1.1 Gated treatment planning and delivery—A more advanced form of free breathing motion management technique for IMPT delivery is the use of respiratory gating. Any of the commonly used respiratory monitoring devices may be attached to the patient. The respiratory gating window is typically set to between 20 to 30% of the breathing cycle around the end-exhale point in the cycle where, ostensibly, the tumor is least mobile. The beam is either manually turned on and off, or, ideally, automatically, by triggering the beam

delivery system. The motion of the tumor within the gating window is substantially reduced. However, the effectiveness of the gating technique relies on the reproducibility of breathing patterns during a single fraction, from one fraction to another, and the correlation between the position of the moving anatomy and the device used as the motion surrogate. Appropriate coaching and monitoring may be used to mitigate these concerns.

As in the case of IMRT, a drawback of gated IMPT delivery is the prolonged delivery time. The prolongation can be reduced somewhat since the 1–2 seconds of time between energy layers may be synchronized with the gate-off period.

5.1.2 Respiratory Management for IMPT Delivery Using Breath Hold—In principle, the breath-hold technique (possibly along with tumor tracking, see below) may be the most effective way of minimizing normal tissue doses while ensuring target coverage. However, breath-hold is often not practical for patients who have compromised lung function. Nevertheless, as for gating, with appropriate coaching and monitoring, breath-hold may be the preferred form of respiratory management for selected patients. Ideally, breath-hold IMPT should be coupled with the respiratory gating system so that the beam is automatically turned on when the patient, viewing his breathing pattern on a monitor, brings it to a specified point (or in a narrow time band) in the cycle and holds it. The beam is stopped when the breath-hold is released. Gated breath-hold technique is more efficient than free breathing respiratory gating.

5.1.3 Tumor Tracking—Another proposed approach to account for respiratory motion is the tracking of the moving target with scanning proton beamlets [93–95]. However, online motion tracking and synchronization is technically highly challenging [96, 97].

Respiratory gating using tracking of implanted fiducial markers is being investigated [98–101]. However, “shadows” created by the markers in the target dose distributions are a matter of concern, which may be mitigated by further development of low atomic number markers.

5.1.4 The Interplay Effect and Rescanning—Rescanning or repainting multiple times with beamlets is an approach to minimize the hot and cold spots produced by the interplay effect in the free-breathing mode of IMPT delivery. In IMPT, there are two types of interplay effect. One is the *intra-energy-layer interplay effect*, which relates to the interplay between tumor motion and the scanning spot during the delivery of a single energy layer. The other is the *inter-energy layer interplay effect*, which deals with the interplay of tumor motion with the changes in energy layers of a beam. The interplay effect for IMPT is more pronounced than for IMRT due mostly to the 3D nature of dose delivery and due to the significant time required to switch from one energy layer to the next in typical delivery systems.

In rescanning, the beamlet visits each volume element in the target multiple times, thus smearing out under- and over-dosage. Rescanning may be carried out randomly without consideration of correlation with the breathing pattern. Such a strategy would require a large number of rescans to be effective and lead to increased blurring at the margins. The potential of repainting/rescanning has been reported by PSI investigators in several publications [86,

102, 103] and by Rietzel and Bert [104]. Alternatively, a “phase-controlled” rescanning may be employed, which combines respiratory gating with rescanning. The delivery of all spots of a given energy layer is carried out within one or more successive gating windows. Multiple scans with phase-controlled scanning minimize the interplay effect. After finishing one layer, the energy is changed and the next layer is irradiated starting with the next gate. An important advantage of this technique is that it reduces the effect of irregular breathing also.

6. Summary

Arguably, IMPT is among the most powerful tools for cancer radiotherapy. Its ability to achieve desired clinical objectives optimally by modulating the intensities of proton beamlets of a sequence of energies can, in principle, achieve unprecedented target conformality and normal tissue sparing Although the use of IMPT began in the 1990’s, only in this decade has this technology started to become widely available. While in the last two and half decades photon radiotherapy has been significantly improved with IMRT and IGRT, corresponding advances specific to IMPT are yet to occur. As proton dose distributions in general, and IMPT dose distributions in particular, are vulnerable to a greater degree to numerous uncertainties than photons and IMRT, many of the advances developed for the latter cannot be directly applicable to IMPT.

In this overview we have identified certain limitations of IMPT as implemented at present and have discussed current and future efforts needed to address them. We believe that, with such efforts, IMPT can be greatly improved to realize its true potential. It is our hope that, with these advances and their clinical implementation, IMPT will become considerably more effective than its current state of the art for many types of cancer and that its efficacy will be clearly demonstrated.

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