Management of Motion and Anatomical Variations in Charged Particle Therapy: Past, Present, and Into the Future

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The major aim of radiation therapy is to provide curative or palliative treatment to cancerous malignancies while minimizing damage to healthy tissues. Charged particle radiotherapy utilizing carbon ions or protons is uniquely suited for this task due to its ability to achieve highly conformal dose distributions around the tumor volume. For these treatment modalities, uncertainties in the localization of patient anatomy due to inter- and intra-fractional motion present a heightened risk of undesired dose delivery. A diverse range of mitigation strategies have been developed and clinically implemented in various disease sites to monitor and correct for patient motion, but much work remains. This review provides an overview of current clinical practices for inter and intra-fractional motion management in charged particle therapy, including motion control, current imaging and motion tracking modalities, as well as treatment planning and delivery techniques. We also cover progress to date on emerging technologies including particle-based radiography imaging, novel treatment delivery methods such as tumor tracking and FLASH, and artificial intelligence and discuss their potential impact towards improving or increasing the challenge of motion mitigation in charged particle therapy.

Keywords: motion management, 4DRT, pencil beam scanning (PBS), particle therapy, proton therapy

INTRODUCTION

The use of charged particles for radiation therapy (RT) represents a valuable treatment paradigm because their unique dose deposition properties, including maximum dose deposition at the Bragg peak and rapid distal falloff, allow for dose to be conformed tightly around the tumor while sparing normal tissues (1–6). However, these advantageous properties present a challenge in the presence of motion, because the same steep dose gradients which provide the benefit of lower integral dose in surrounding tissues are vulnerable to even small displacements in the patient geometry. In addition, because their range is dependent on tissues along the beam path, charged particles traveling through heterogenous tissues (such as in lung cancer) also suffer from dose deviations due to motion-induced range uncertainties (7).

Proton therapy is by far the most widely implemented form of charged particle therapy, with forty-one proton centers operating in the US and ninety-nine centers operating worldwide (8). Initial proton therapy systems were based on passive scattering, in which a scattered beam is passed through a range-modulating wheel [to determine the width of the spread-out Bragg peak (SOBP)] and a custom collimator and compensator (to laterally shape the beam and match the distal edge of the SOBP to that of the patient target). However, this scattering method is limited in its ability to conform dose to the proximal boundary of the target (9). Over time, a pencil beam scanning (PBS) method was developed which exhibited improved dose conformation around the target in comparison to passive scattering methods; dosimetric benefits of proton PBS have been verified across a diverse range of disease sites, including brain, esophageal, oropharyngeal, breast, and liver cancers (3, 6, 10–14). Proton PBS is performed by scanning a monoenergetic pencil beam over a grid of positions and repeating for multiple beam energies to create a SOBP with a varying span along the lateral direction. Treatments using PBS delivery utilize intensity modulation of the pencil beam spots and are optimized using one of two planning techniques. Single field uniform dose (SFUD) planning refers to a planning technique in which pencil beam weights are optimized independently for each field according to the planning objectives, resulting in treatment plans where each field contributes similar tumor coverage. Multi-field optimization (MFO) is a planning technique in which the pencil beam weights of every field are optimized simultaneously. Of these two planning methods, SFUD is more robust against motion because it only requires the consistency of anatomy during the treatment delivery of its own field. MFO requires the integrity of anatomy during the entire treatment session from all treatment fields; therefore, the potential impact of motion is more significant. PBS-based proton therapy is often referred to as intensity-modulated proton therapy (IMPT), which is created by simultaneously optimizing the beam intensity and energy for each spot/delivery unit. The addition to range uncertainties and sensitivity due to steep dose gradients at the distal end of the target, proton PBS presents an additional challenge for precise dose delivery under conditions of motion due to interplay effects between the scanning beam and intra-fractional motion in the patient anatomy (5, 15). The interplay of the proton and ion pencil beam scanning and organ motion has been shown to impact the target dose coverage in multiple disease sites (16–19). Recent lung cancer simulation studies found that interplay effects combined with small spot sizes (~3mm) resulted in a loss of 2-year local control of up to 18.5% ± 25.2% compared with the static cases for single fraction delivery; for multi-fractionation treatment significant loss of local control was observed only for large motion amplitudes (>30mm) (16). For esophageal cancer, a recent planning study found PBS proton therapy plans using posterior beams to be more robust against underdosage (V95% $_{CTV}$ <97%) in comparison with IMRT, but interplay effects had an increasingly negative impact on the dose distribution as the number of simulated fractions was decreased below 10 (17). As the beam delivery time structures and intensities from various charged particle accelerators such as synchrotron or cyclotron are different (20), they can result in different interplay effects (21).

As of 2021, there currently exist twelve operating carbon-ion treatment centers with five more under construction (8, 22). Similar to protons, carbon and other heavier ions such as helium exhibit highly localized dose deposition at the Bragg peak. An additional advantage of treating with carbon ions (over photons and protons) is that they exhibit steeper lateral penumbra and higher linear energy transfer (LET), leading to increased relative biological effectiveness (RBE) (23). Like protons, carbon ions can be delivered either *via* passive scattering or pencil beam scanning; however, largely due to cost the majority of centers perform only fixed beam delivery, with only two capable of a full range of treatment angles through rotating gantry (24). A challenge of treating with carbon and other heavy ions is that the increased sharpness of the lateral penumbra in combination with the Bragg peak results in heightened dose uncertainties in the presence of motion. In addition, because carbon ions exhibit a distal tail of dose beyond the Bragg peak due to nuclear fragmentation, the potential for dose uncertainties distal to the target volume are of greater concern (24). Additionally, for carbon and heavier ions, RBE is nonlinear with respect to the absorbed dose level, particle energy, and atomic number (25), thus while it is typical to consider a constant RBE for proton radiotherapy (26), when considering the carbon ion interplay effects, the changing RBE along the beam path should be taken into consideration.

Motion management refers to techniques in RT which seek to mitigate the effects of inter- and intra-fractional motion. Causes of inter-fractional motion include weight loss, tumor shrinkage, and organ deformations such as those caused by changes in the volume of the rectum and bladder (27, 28). Inter-fractional motion occurs between fractions, typically separated by hours or days, and thus if correctly identified can be corrected with an established adaptive planning process. Intra-fractional motion is the result of respiration and to a lesser extent cardiac motion and peristalsis. Because intra-fractional motion occurs during treatment on a timescale of minutes to seconds, it represents a greater challenge. Imaging and treatment planning modalities which take into consideration time in addition to the 3-dimensional space of the patient are commonly referred to as 4D (e.g., 4DCT and 4DRT).

Motion management can generally be categorized into one of two strategies: 1) prevent or reduce anatomical motion, or 2) adapt treatment to motion during planning or delivery. The success of these strategies depends on access to imaging techniques which allow motion and/or dose deposition to be faithfully monitored and quantified. While much work has been done to address challenges in motion related to charged particle therapy, currently there is limited standardization of treatment protocols, with many centers developing their own unique standard of procedures and best practices (29). For example, in the case of proton therapy for thoracic cases, the Particle Therapy Co-Operative Group (PTCOG) Thoracic and Lymphoma Subcommittee has begun the work to define a set of guidelines

for best practices, but stress that it is still necessary for institutions to determine their own protocols, due to variations in technology across institutions as well as lack of commercialization for many solutions (9). Recommendations for control at other treatment sites are scarce.

This review seeks to provide an overview of current clinical practices for intra- and inter-fractional motion management in charged particle therapy as well as progress to date on emerging technologies that have potential to be used for or impact motion management. The remainder of this review is organized as follows: Section 2 provides an overview of the current state of the art in motion management implemented in clinical charged particle therapy, including motion reduction techniques at the major anatomical sites, imaging techniques for monitoring intra- and inter-fractional motion, as well as treatment planning, delivery, and plan evaluation mitigation strategies; Section 3 discusses promising ongoing research and emerging technologies in charged particle therapy which will either directly benefit or necessitate further innovations in motion management.

CLINICAL IMPLEMENTATION: THE CURRENT STATE OF THE ART

Motion Control Techniques at Simulation and Delivery

Motion control techniques consist of methods which seek to reduce patient motion and ensure consistent geometrical orientation during and between fractions.

Thorax and Upper Abdomen

In the thorax and upper abdomen, respiration is the most significant cause of intra-fractional anatomical variations. In thoracic tumors, motion control methods for proton therapy are recommended when a patient's target motion amplitude exceeds a pre-determined threshold (established per institution based on target location and treatment parameters) (9). Breath-hold is a standard technique for minimizing respiration-based movement during treatment delivery to the thorax and abdomen. Breath-hold involves patients temporarily suspending respiration at specific, reproducible lung volumes. Breath-hold techniques can be classified as *voluntary*, in which the patient is in control of their breathing (30), or *active*, in which the patient's airflow is temporarily blocked by a valve (31). A widely used commercial voluntary breath-hold system is the SDX Respiratory Gating System (DYN'R Medical Systems, Toulouse, France). The SDX system monitors the inspiration and expiration volume of a patient in real-time and provides visual display of the breathing-trace through patient-worn goggles. This allows the patient to perform consistently reproducible breath-holds at a specific volume for a specific duration of time. Typically, for thoracic cases, deep inspiration breath-hold (DIBH) is preferrable (holding in a deep breath at an individually determined volume threshold) because this increases the distance between the tumor and organs at risk. DIBH proton treatments to Hodgkin lymphoma and left breast

cancer have shown significant reduction in lung and heart dose compared with the photon plans (32–34). High frequency percussive ventilation (HFPV) is an example of an active breath hold technique. In HFPV, the patient receives high frequency pressured pulses of air, causing suppression of respiratory motion and allowing for longer breath-holds. A drawback of HFPV is the requirement of anesthesia support, which may not be always available in radiation oncology. A recent study has also reported on the use of an enhanced deep inspiration breath hold (eDIBH), which involves passive, patient-controlled breath holds aided by preoxygenation, hyperventilation, and patient coaching to increase breath-hold times. eDIBH was found to reduce variability in lung volume and position in comparison with HFPV (35). Not all patients are candidates for breath-hold techniques. Patients with impaired respiratory function typical of advanced lung cancer may be physically unable to tolerate breath holds, while younger patients may be unable to follow instructions for voluntary breath-hold. Another limitation of breath-hold based motion management is it cannot account for inter-fractional anatomical changes, such as tumor shrinkage and lung density changes which can result in changes to the water equivalent path length (36).

Abdominal compression (AC) belts are a relatively inexpensive and easy-to-implement option for minimizing intra-fractional motion from respiration. For charged particle therapy, thin belts made of homogenous materials are preferred to ensure that the belt has a minimal and reproducible impact on the charged particle range (37). For PBS proton therapy, the use of AC has been shown to be valuable for reducing moderate to large motion during treatment of liver tumors (37, 38). Additionally, AC in combination with layered rescanning and respiratory gating has been clinically adopted for motion mitigation in carbon ion therapy (39). A limitation of compression belts is that the degree of compression applied is limited by individual patient tolerances, with some patients are unable to tolerate abdominal compression during treatment. The compression belt typically has fiducial markers and pressure meter to ensure consistent positioning of the belt during treatment. Nonetheless, it is recommended to avoid having particle beam passing through the device to avoid potential water equivalent thickness (WET) variations in the setup (38).

Lower Abdomen and Pelvic Regions

For the lower abdomen and pelvic regions, positioning techniques focus on reducing motion caused by volume changes in the rectum and bladder. Consistency of the position of bladder and rectal volume across and during treatment can be improved through hydration and voiding schedules (40, 41). Rectal balloons are used to immobilize the prostate and maintain the rectum at a consistent volume during simulation and treatment, reducing uncertainties from variable rectal filling and gas and allowing for smaller target margins and greater sparing of the rectum during external beam radiotherapy (42). For charged particle therapy, rectal balloons are inflated with water instead of air to maintain a consistent water equivalent pathlength (41); this removal of the rectal air cavity likely reduces the dosimetric benefit to the anterior rectal wall which is seen

with the air-based inflation used in photon therapy (42, 43). Recently, a rectal biodegradable hydrogel that is implanted between the prostate gland and the rectum was implemented in the clinic. For proton radiotherapy, the use of hydrogel provided improved rectal sparing and decreased late gastrointestinal toxicity compared with the use of a rectal balloon, suggesting that motion due to moderate rectal filling does not require intervention if adequate separation (8-13mm in this study) between prostate and rectum is achieved (44).

Imaging at Simulation and Delivery

Imaging technologies play a pivotal role in motion management for radiation therapy, allowing for the contouring of structures for treatment planning and providing a means to assess and monitor organ motion, either directly by imaging the motion of organs or *via* indirectly by imaging markers placed in tissue, e.g., fiducial markers. Computed tomography (CT) images are the gold-standard modality for treatment planning; however, CT images acquired during free breathing can suffer from motion artifacts, leading to uncertainty in the true delineation of boundaries between tumor, normal tissues, and organs at risk (45). For this reason, 4D computed tomography (4DCT) images, in which a series of CT images are acquired during different phases of the breathing cycle, have become a standard in treatment planning for thoracic and abdominal regions. One limitation of 4DCT is that irregularities in patient breathing during image acquisition leads to inherent uncertainties in how faithfully the final 4D images represent the patient's anatomy during respiration. Patients can also exhibit variations in their breathing cycle during day-to-day treatment; the intra-fractional motion patterns from respiration can themselves be subject to inter-fractional variations. For proton PBS therapy, weekly offline CT assessment are recommended for patients expected to experience inter-fractional changes (9). Because not all commercial treatment planning software supports multi-image planning, information from the 4DCT can be utilized for treatment planning by transforming the series of images into a single "representative" view of the patient, such as average intensity projection (AIP), maximum intensity projection (MIP) and mid-ventilation (MidV) (46).

Simulation for proton therapy treatment planning often involves fusion with tissue function-related positron emission tomography (PET) and magnetic resonance imaging (MRI) for target delineation. 4DPET provides information on tumor motion in addition to the metabolic information about the tumor structure and has been shown to be a valuable tool for target delineation in lung cancers (47). 4DMRI provides high contrast of soft tissues and has shown promise for motion-robust target delineation in both abdominal and lung cancers (48–50). A recent study further used 4DMRI and 3DCT to generate synthetic 4DCT for 4D dose calculation and interplay effect evaluation in pancreatic cancer (51).

Conventional cone-beam CT (CBCT) was first implemented for proton therapy for patient setup in 2012 (52). Daily CBCT adds valuable 3D anatomy information and soft tissue contrast in patient setup alignment compared to 2D kV imaging. It can also

be used to identify inter-fractional tumor regression, weight loss, organ filling or atelectasis. Efforts have been made to enable CBCT for online adaptive planning for proton therapy (53–56), but it suffers from reduced image quality in comparison to CT due to restricted field of view, lower soft-tissue contrast, and inequivalent relation between CBCT voxel values and Hounsfield units. CT-on-Rails has also been investigated as an alternative to daily CBCT imaging for daily adaptive radiotherapy due to its ability to provide higher quality images at "near-treatment-position", though widespread adaption of CT-on-Rails is limited due to increased cost and larger footprint (57). Interested readers can find an in-depth discussion on radiological image guidance in particle therapy in the recent review by Landry and Hua (58).

Internal tumor motion during delivery can be monitored through implanted markers, such as electromagnetic sensors (59–61) and fiducial markers (62), with externally placed detectors. A benefit of EM systems or on-board imagers is that they do not require line-of-site and can thus also capture signal from internally placed markers. Tang et al. have used electromagnetic transponders to assess the intra-fractional prostate motion during PBS SFUD delivery (63). A major limitation of electromagnetic systems is that they are sensitive to distortions of the generated electromagnetic signal; a recent study found EM tracking systems unable to provide clinically useful measurements during proton therapy in the presence of gantry motion or when too close to a CT scanner (61). In addition, caution should be taken in the selection of the implanted markers for proton therapy to avoid image artifacts and dose disturbance (64).

Fluoroscopy with implanted markers can produce 2D images with high spatial and temporal resolution. Researchers at Hokkaido University in Japan have pioneered the clinical implementation of a gated proton PBS treatment system that utilizes fluoroscopy for real time tumor tracking through an internally placed gold fiducial marker (65–67). Aside from requiring an invasive placement, a potential risk is that the fiducial marker could migrate from its original placement during the course of treatment (68).

Another strategy for assessing tumor motion is to measure the patient's surface motion, which can then be used as a surrogate to infer the position and movement of the internal target (69). Surface imaging uses cameras/projectors mounted in the treatment room to capture pseudo-random light patterns projected on the patient surface to derive the patient surface change. It is non-ionizing and can monitor a large surface constantly from a distance; thus in addition correcting for inter-fractional motion during daily positioning, surface imaging is an attractive option for monitoring intra-fractional motion (70). A reported challenge of surface imaging in a clinical proton setting is that the layout of the therapy room can lead to restricted field of view or occlusion of the surface cameras at treatment gantry angle (71). Clinical applications of surface imaging for daily positioning of breast cancer proton therapy patients have been reported and found to achieve similar dosimetric accuracy to daily CBCT (70–72); however it was

noted that surface imaging alone can be insufficient to detect internal shifts of breast implants (71). Further surface imaging studies have noted limited correspondence between measured surface motion and internal target motion (73–75). Nevertheless, a recent technological assessment showed that optical tracking has better potential than electromagnetic tracking of embedded fiducial markers for use in PBS proton therapy (61).

Treatment Planning and Delivery

Many different strategies exist to account for patient motion during the treatment planning process or delivery itself. Mitigation during treatment planning and delivery is characterized by an approach of working with or around existing patient motion. These strategies rely on additional information input from imaging, either during simulation (in the case of treatment planning) or in real time during treatment delivery.

Motion-Encompassing Margins

One of the most widely used planning methods to account for expected patient motion in charged particle therapy is to delineate an additional margin around the tumor target, commonly denoted the internal target volume (ITV), which is defined as the overlay of boundaries for all (or a select subset of) CTV positions collected during 4DCT (76). While the use of ITVs alone is not considered adequate for motion management in PBS proton therapy due to range uncertainties and interplay effects, ITVs are recommended for use in combination with other motion mitigation strategies to account for any residual motion uncertainties (77). For example, for patients being treated with breath-hold, several breath-hold CT scans are performed during simulation to create an ITV that encompasses the variability of the breath-hold position for a particular patient. ITV structures can also be used in conjunction with compression belts under conditions of free breathing to account for residual motion. ITVs can be constructed using different methods based on 4DCT images, including Max/Min inhale-based, MIP-based, and MidV-based. In addition, the concept of using density overrides within and around the ITV has been shown in recent simulation studies to improve dose coverage when the target moves through regions of highly variable density (78, 79). Once an appropriate ITV has been determined, additional population-based margins reflecting setup and beam-specific range uncertainties are applied to generate a planning target for each beam (80).

Repainting

A unique challenge for particle therapy in the face of intra-fractional motion is the additional dose uncertainty caused by interplay effects between patient anatomical motion and the delivery sequence of the scanning beam. A mitigation method is to use repainting, which refers to a treatment delivery method applied for PBS by rescanning over the same spot positions multiple times (using an appropriately lower fraction of monitor units defined by the total number of repetitions) (81, 82). Studies on repainting for PBS proton therapy have found that this method improves dose homogeneity; however, interplay effects

were found to be more pronounced for small tumor sizes, motion greater than 10mm, and small spot sizes (83, 84). Another recent study demonstrated that interplay effects due to motion could be further reduced using a novel repainting strategy in which the repaintings for a given energy layer (and by extension the repaintings for each spot position) are spread out evenly over the entire breathing cycle (85). This was accomplished by designing a flexible delivery schedule in which the number of times a given spot is repainted as a function of its assigned MU and the time it takes for the scanned beam to reach the given spot from its previous position, such that: 1) each spot is repainted as many times as possible, 2) repaintings for each spot are spread evenly over the breathing cycle, and 3) the total time to deliver a given energy layer is constricted to the length of the breathing cycle. One challenge for the repainting strategy is that it may encounter the minimum MU requirements because it requires the delivery of a smaller amount of dose multiple times. Sometimes it may only be possible to repaint the distal layers because they usually receive more dose.

Beam Angle Selection and Spot Size

In treatment planning, beam angle selection can help to minimize dose deviations by selecting beam orientations that are robust to motion. Proton range is sensitive to tissue variations along the beam path. Movement can cause tissue variation uncertainties that lead to dose deposition uncertainties. Thus, in selecting beam angles for proton therapy, it is advantageous to avoid large tissue density gradients in the beam path and to try to keep the beam angle parallel to the dominant direction of tumor motion (9). It is also important to avoid beam orientations such that the distal fall-off region of the proton range proximally borders an OAR, as range uncertainties could lead to unintended overdosing OAR or underdosing the CTV. Specific protocols for the selection of beam angles have been found to vary across facilities, but nevertheless follow these guidelines discussed above (76).

The pencil beam spot size, defined as the full width at half-maximum of the beam spot in air, has been identified as an additional beam parameter that impacts dosimetric deviations in PBS proton therapy (16, 63, 76). Specifically, larger spot sizes (~13 mm) have been shown to reduce the interplay effect compared with smaller spot sizes (~3mm) (16).

Respiratory Gating

Respiratory gating is a dynamic treatment delivery method used to ensure precise dose deposition in the presence of respiratory motion. In this technique, the treatment beam is turned on only when the patient is in a specific phase of their respiratory cycle. Gating methods can be performed in conjunction with breath-hold techniques or during free breathing; clinical use for charged particles has been described for several disease sites, including the lung, breast, and liver (86–89). Implementation of gating relies on the ability to accurately monitor patient motion during treatment delivery and on the ability for patients to perform reproducible breath holds or reproducible free-breathing cycles. Motion monitoring for charged particle gating is typically accomplished *via* external surface imaging (90). For PBS

proton therapy, a gating approach to treatment delivery in conjunction with real-time fluoroscopy imaging has been implemented and shown *via* simulation studies to be capable of significantly reducing mean liver dose while providing better target coverage in comparison with a free-breathing approach (66, 91). A limitation of beam gating for PBS-based therapies is that they can still suffer from interplay effects due to residual motion during the selected gating window; recent simulation studies suggest this can be mitigated through the use of laterally and longitudinally overlapping pencil beams or phase-controlled rescanning (92, 93). Another reported challenge to the clinical use of gating for PBS is balancing the gating window width with the duty cycle (ratio of beam-on time to overall treatment time). While a narrower window width provides improved motion mitigation, it can also lead to unacceptably long treatment times. A recent simulation study for PBS-based gated therapy of liver tumors found duty cycle dropped by as low as 10% when a small window width (3mm) was used for a gating-only approach (94). Gating in combination with repainting has been shown to be more efficient in motion mitigation than repainting alone (94, 95). Another challenge of implementing gating for proton therapy is that proton systems are subject to latency in beam control, meaning once a gating signal is detected from the patient, the treatment machine requires a delay to turn-on or turn-off the beam. This delay can sometimes be too long (150-200 ms in a 3-4 s breathing cycle) to perform reliable cycle-to-cycle beam delivery. For this reason, respiratory gating in particle therapy is usually performed in conjunction with breath-hold techniques, which provide a longer treatment window such that the beam's gate-lag time is insignificant.

4D and Robust Optimization

In radiation therapy, robust optimization (RO) can be used during the treatment planning process to design plans which are robust to the uncertainties associated with treatment delivery, including setup errors and patient motion. Traditionally for photons, such uncertainties in treatment planning have been accounted for by using an expanded margin around the CTV, called the planning target volume (PTV). In proton therapy, the additional presence of range uncertainties and, in the case of PBS, uncertainties from the interplay effect render the use of traditional margin-based solutions insufficient.

3DRO refers to a class of robust optimization techniques which account for patient setup and range uncertainties during treatment plan optimization. Implementations of 3DRO include probabilistic treatment planning, scenario-wise mini-max RO, and voxel-wise worst-case RO. In probabilistic optimization, setup and range uncertainty scenarios are randomly sampled from an assumed probability distribution to produce a large set of potential dose distributions (96, 97). This method is computationally expensive and requires prior knowledge of the probability distributions of the treatment conditions. Scenario-wise mini-max and voxel-wise worst-case RO evade these challenges by performing plan optimization based on either a smaller set of worst-case scenarios or a single worst-possible dose distribution (98–100). 4DRO can be considered an extension of 3DRO in that it also considers intra-fractional variations caused

by organ motion such as respiration. Recent simulation studies have shown promising benefits of 4DRO for scanning proton therapy, including improved target coverage and improved robustness against interplay effects (100–102). In a study by Ge et al. comparing the performance between 3DRO and an in-house 4DRO system on a set of 10 lung cancer patients treated with IMPT, the 4DRO system was found to outperform both 3DRO and traditional PTV-based optimization methods in terms of dose homogeneity, CTV target coverage, and dose robustness considering setup uncertainties and patient motion (100). Another recent study published by Mastella et al. looked at the incorporation of gating with 4DRO for 20 lung cancer patients found that this 4DRO optimized gating approach resulted in significant reduction to lung dose while maintaining target coverage (102).

Studies have been performed for carbon ion 4D dose reconstruction and optimization. Reconstruction of the delivered 4D RBE dose needs to consider the tumor motion and temporal structure of the beam delivery (103). Eley et al. (104) worked on a 4D optimization approach for scanned beam tracking to reduce the dose to organs near the moving target. Graeff et al. (105) proposed a 4D optimization scheme that divides the target into sectors and to each of the sector with a delivers dedicated raster field corresponding to individual motion phases. Expanded carbon ion 4D-IMPT including the robust non-linear RBE-weighted optimization was also included (106, 107). For clinical application, it is essential to consider both the 4D treatment planning systems and 4D treatment control systems (108). 4DRO is currently commercially available through the RayStation treatment planning system (RaySearch Laboratories, Stockholm, Sweden) (109).

Plan Evaluation

Due to the interplay effect in proton PBS delivery, special considerations should be taken in evaluating PBS proton plans to ensure that the intended dose distribution can be delivered faithfully under conditions of anatomical motion. The guidelines provided by the Particle Therapy Co-Operative Group (PTCOG) Thoracic and Lymphoma Subcommittee recommended the use of a 4D phantom to evaluate motion interplay effects and the effectiveness of planned motion mitigation techniques, though at this time such a protocol is admittedly out of reach for most centers due to the expense of 4D phantoms (9), which have only recently become commercially available. In the same publication, the importance of continuous plan evaluation (through regular repeat 4DCT scans) to assess the need for plan adaption is also emphasized. Meijers et al. reported on a 4D dose reconstruction method which utilizes weekly repeated 4DCT scans in combination with treatment log files and breathing pattern records from each fraction (110, 111). This dose reconstruction method can be used to calculate dose accumulation on a per-fraction basis, allowing the clinical team to monitor motion-based dose degradation over the course of treatment and to help to trigger adaption when necessary. Recent studies have also reported on the implementation of tools designed for evaluation of PBS proton plans for moving targets. For example, Riberio et al. reported on the development and application of a plan

evaluation tool, 4D robust evaluation method (4DREM), which considers both setup errors as well as respiratory motion and the interplay effects (112), while Korevaar et al. developed a scenario-based plan evaluation method which allows for comparison between photon and proton plans (113). In another hand, fast 4D dose calculation with GPU-accelerated dose-engines enable potential clinical use and can be integrated into the optimization process (114–116). Another consideration for 4D dose calculation is that the temporal resolution used can impact the calculated final accumulated dose distribution, a recent simulation study found that the use of finer temporal resolutions for 4D dose calculations can help to reduce the over-estimation of interplay effects for hypo-fractionated treatments (19).

FUTURE TECHNOLOGIES

Advanced Imaging Techniques

A major directive in motion management is to develop methods that allow for high quality *in vivo* observation of internal anatomic structures during treatment fractions. 4D-CBCT has been recognized as a promising emerging technology in identifying intra-fractional motion at the time of treatment and has been investigated for photon therapy (117, 118). This technology potentially reduces the motion artifacts associated with 3D-CBCT and can be used for tumor motion verification when comparing with the planning 4DCT (119). Currently, there is a trade-off between image acquisition time and image quality, making it challenging for fast and reliable adaptive tumor target delineation and motion analysis with 4D-CBCT. Research investigations of image processing methods to improve 4D-CBCT image quality with reduced scan times are underway (120–123), and the commercial development of a dual-imaging proton treatment system with 4D-CBCT capability has been announced by Hitachi, with approval of the Japan's Pharmaceuticals and Medical Device Agency (PMDA) granted in 2020 (124).

Other imaging approaches provide promising alternatives for *in vivo* monitoring of anatomical changes and assessment of range uncertainties. One such developing imaging method for charged particle therapy is ion-based radiography, such as proton radiography (PR). PR involves measuring the residual energy of high energy protons after they have passed through the patient to construct a 2D image where each pixel represents the WET of the patient along the beam path at that position. PR has been proposed as a tool for quality control through *in vivo* proton range verification, as an aid for pre-treatment patient positioning, and even as a means to guide online plan adaptations (125, 126). The characterization of the WET accuracy, noise, and spatial resolution of a commercially developed prototype for clinical PR were reported (127, 128). Another PR system which measures individual proton depth-dose curves *via* a multi-layer ionization chamber was introduced and used to measure range uncertainties in proton pencil beams in a 4D porcine lung model; the findings supported the use of 3%

range uncertainties for robust treatment planning in thoracic regions (129, 130). Proton-based fluoroscopy has also been proposed, and was investigated for range verification and monitoring of inter- and intra-fractional motion in lung tumors in a recent simulation study (131). Helium and carbon ion-based radiography systems have also been investigated in simulation and experimental studies, with carbon ions achieving the highest image quality at the cost of increased dose (132–134). A benefit of ion-based radiography is that it requires less dose in comparison with conventional x-ray radiography due to low fluence requirements and the Bragg peak not contributing to patient dose. A limitation of ion-based radiography is that particles must be able to fully penetrate the patient to acquire an image. Current clinical therapy systems can achieve a penetration depth of ~30cm, which may be insufficient for large patients for certain beam directions.

MRI-guided radiotherapy is an exciting imaging strategy for *in vivo* motion management during treatment because in addition to being non-ionizing, it provides excellent soft tissue contrast, high temporal resolution, and is capable of functional imaging (135, 136). While it has already been implemented for photon radiotherapy *via* the MR-linac, the application to charged particles is currently challenged by the need to mitigate the deflection of the treatment beam by the beamline magnetic field. Modelling on MR-integrated proton therapy for liver cancer has shown clear dosimetric benefits as well as significant reduction in normal tissue complication probability in comparison with other imaging modalities, including offline MR-guided proton therapy and MR-linac (137). Recent studies have made progress in quantifying the impact of the magnetic field on detectors for proton dosimetry and demonstrating the technical feasibility of low-field MR guidance on phantoms in a static research beam line (138, 139). Additional studies have investigated methods for calculating stopping power ratios from MRI to generate an MRI-based "synthetic" CT image for treatment planning and range verification (140). The first clinical MRI-proton system is scheduled to be built in 2022 at the OncoRay – National Center for Radiation Research in Oncology in Dresden, Germany (141).

Motion changes the ion beam path and alters the beam range. *In vivo* ion beam range can be potentially monitored by secondary particles generated during nuclear reactions of the ion beams with tissue (142). One set of the nuclear processes generates position emitters which annihilates into 511 keV photon pairs. Several in-beam PET designs were proposed to detect the proton range (143, 144). Its potential to assess the proton and carbon ion beam ranges was studied (145, 146). However, the limited PET spatial resolution and the biological washout of the nuclear activation confounds the analysis of the range from the PET images. Nonetheless, reconstructed time-resolved activities indicates its potential for online range verification during treatment (147).

Prompt gamma (PG) imaging is a technology that allows for *in vivo* proton range verification (on a spot-by-spot basis) during treatment delivery through the measurement of gamma rays created from nuclear interactions with protons passing through tissue.

The *in vivo* human applications of prompt gamma with passive scattering and PBS proton beams were reported (148, 149). One challenge of implementing PG imaging is that the number of photons needed to create a reliable signal (~10^8) exceeds the number of photons generated in most pencil beams for RT treatment. Potential solutions to this challenge include re-optimizing the treatment plan such that several of the pencil beams are boosted to reach this counting threshold, or aggregating the statistics from multiple neighbour pencil beams (at the cost of reduced resolution) (150). A recent simulation study by Tian et al. demonstrated under conditions of inter-fractional motion that a selective spot boosting method achieved tight <0.8 mm PG-dose correlation. This study further supports its proposed use for proton range monitoring (151).

Detection of the secondary charged particle emission in light-ions such as carbon ion beams was also proposed for beam range monitoring purposes (152); the capability of using charged secondary emission profiles to track ion beam range, spot position, and internal motion has been demonstrated in recent simulation studies (153, 154). It is realized by back-tracking and reconstructing the profile of the secondary emissions (155). The use of charged particles to detect lateral pencil beam position to a resolution of millimeters was reported recently in anthropomorphic head and neck phantom using a carbon ion beam (156). The INnovative Solutions for In-beam Dosimetry in hadronthErapy (INSIDE) collaboration has recently reported on the clinical trial for a carbon ion beam-range monitor and demonstrated the potential of this system to detect inter-fractional beam range variations which could be used to trigger re-simulation and adaptive replanning (157).

Another emerging technology for *in vivo* range verification is protoacoustics. Protoacoustics works by measuring the thermoacoustic pressure waves generated by the energy deposition of therapeutic protons in tissue. Like prompt gamma, protoacoustics is an attractive option for range verification in that it is derives its signal from the treatment beam itself, essentially utilizing free information from the patient's internal anatomy without the need for additional dose. In addition, a protoacoustic system can be implemented at low cost compared with other methods (158). Currently, the primary challenge in implementing protoacoustics as a mainstream technology is to develop methods for rapid and accurate translation of the acoustic pressure signal in heterogenous tissues into meaningful information about proton range, which is an active area of research (159, 160). Further work has also been done to characterize the dependencies of the protoacoustic signal on the proton pulse shape (161).

Novel Delivery Methods

Tumor tracking or "beam tracking" in radiotherapy refers to a delivery method in which the tumor position is actively tracked, and the treatment beam is modified in real-time to correct for intra-fractional motion. It has been described by previous reviews as one of the most promising but also the most technically challenging motion mitigation strategy for charged particles (162–164). Although tumor tracking has been achieved in the clinic for photon therapy, clinical implementation has yet to be realized for scanned ion beams due to additional technical challenges presented by charged particle treatment regimes. Unlike photon therapy in which tumor tracking can be achieved in the beam's eye view, tumor tracking with scanned ion beams requires 3D information as well as the ion beam delivery system's ability to change beam energy rapidly. Specifically, both the beam position and beam energy need to be rapidly modified to account for changes in the location of the tumor as well as the changes in the beam range caused by variations in depth and/or tissue composition in the beam path. Simulation studies have evaluated the robustness of tumor tracking systems for both carbon ion and proton scanned beams (165, 166). Ultrasound-guided tracking systems have also been explored (167, 168). Efforts have also been made to explore a motion-synchronized dose delivery system for ion therapy which carries the benefits of tumor tracking without the difficulties of implementation (169). In their study, Lis et al. created a 3D treatment plan on each of the 4D breathing phases. With anatomic motion monitoring, dynamic switching between plan libraries for tracking dose delivery was realized through an adaptive layer of software and hardware interfaces. Preliminary tests revealed acceptable dosimetric performance and safety characteristics. The system has the potential to deliver conformal, motion-compensated doses to the moving target.

Various novel beam setups have been proposed to aid in charged particle motion management. The use of a dual carbon-helium ion beam was proposed for carbon ion treatment with helium-guided imaging for range verification (170, 171). The rationale is that for a given energy, helium ions exhibit a range about three times that of carbon ions. This, in conjunction with the fact that both ions have approximately the same charge/mass ratio, means that both ions could be accelerated together in a synchrotron and delivered simultaneously, with the carbon depositing dose in the patient and the helium passing through the patient to a detector to provide online range estimation. Simulation studies using mixed beams have demonstrated the ability to detect range changes as small as 1 mm and detect changes in simulated rotations and bowel gas movement in anthropomorphic phantoms (172). Another novel beam delivery method is the use of radioactive ion treatment beams such as ^{11}C and ^{15}O, which could be utilized for improved PET imaging to achieve more accurate online range verification (173). Finally, patient orientation with respect to the ion beam can also be considered for reducing motion. Patient setup using an upright treatment posture has also been shown to reduce thoracic motion while increasing lung volume, and has been suggested as a potential motion mitigation strategy for lung cancer patients who cannot tolerate DIBH (174). A limitation of upright radiotherapy treatment posture is that for patient simulation it necessitates using a vertical CT to ensure accurate localization of anatomy between simulation and treatment; currently upright treatment of charged ion beams is limited to only a few centers (175).

Just as the evolution of proton therapy from passive scattering to scanned beam delivery presented new challenges in handling patient motion, future advancements in charged particle

treatment delivery will necessitate new innovations to ensure patient safety in the face of motion. One promising emerging radiation technology is FLASH radiation therapy. Defined as radiation therapy delivered in ultra-high dose rates (>40Gy/s), FLASH RT has been shown for *in vivo* animal models to achieve less toxicity for normal tissues while providing the same degree of tumor control (176–179). Multiple platforms (180) including proton clinical machines (181, 182) were able to generate FLASH beams, but biological and technological challenges remain to realize clinical FLASH delivery. Further work on understanding the FLASH mechanisms, as well as optimal treatment dose, dose rates, and fractionation scheme needs to be established (183–185). Shortened treatment delivery times resulting from FLASH dose rates would potentially alleviate concerns about intra-fraction motion, but this also means that any unaccounted-for setup uncertainties and motion will likely lead to the dose being delivered to a completely unexpected location with no opportunity to be mitigated. Thus, the FLASH treatment paradigm necessitates a revisit on current clinical motion management practice and the exploration on the limits to ensure safe and accurate dose delivery when considering the "snap" of motion during ultra-fast dose deliveries.

Arc therapy is an emerging technology in proton therapy in which the gantry is rotated continuously through a pre-selected arc during treatment delivery. ARC therapy for photons (VMAT) is a standard clinical tool with several different commercial systems available (186). In 2021, the commercial proton therapy vendor IBA announced a global DynamicARC consortium, signaling a shared commitment between industry and select clinical centers towards translating proton arc therapy into a commercially available system in the near future (187). While proton ARC therapy has yet to be adopted into standard clinical practice as of yet, its application has been investigated and shown promise in reducing treatment delivery times, improving dose conformality, and reducing dose to OARs in multiple treatment sites (188–190). Planning study was also performed for carbon-ion beams to show normal tissue sparing and mitigation on the hypoxia-related tumor radioresistance (191). Robustness against range uncertainties using proton ARC therapy was demonstrated (192, 193). However, a potential drawback of proton ARC therapy is that it results in increased low dose/low LET dose to normal tissues, which could increase the risk of secondary cancers (194). Different treatment delivery scheme and dose distribution in ARC therapy from traditional PBS delivery will need further studies to assess potential interplay between patient motion and the rotating treatment beam.

Artificial Intelligence

Artificial intelligence (AI) refers to technologies or machines which can perform tasks/calculations with human-like skill and cognition. Machine learning (ML) is a subcategory of AI relating to computer algorithms which can "learn" to perform a task without being explicitly programmed to do so. Machine learning, and in particular deep learning (DL), has found tremendous success in the past decade in many diverse fields, ranging from finance to automotive technologies, and to medicine (195). DL (also called deep machine learning) is a specific class of ML algorithms which is capable of learning higher-order abstract representations or "features" from raw input data, as opposed to classical ML algorithms which learn patterns from user defined ("handcrafted") features (196). There is no known theoretical basis for the required structure of an algorithm to achieve DL; in practice however, artificial neural networks, which by design perform a nonlinear mapping from input data to the desired output space, have achieved the best success to date. In radiation oncology, machine learning and deep learning have seen exponential growth in applications and are poised to revolutionize the field (197).

Deep learning applications have been investigated for inter-fractional motion management in charged particle therapy. Van der Heyden et al. presented a single detector, multi-energy proton radiography system which relied on artificial intelligence to filter out proton scatter (198). In addition, multiple studies have been reported which utilize deep learning as a tool to facilitate accurate proton dose calculation from daily CBCT images (121, 199–201). Elmahdy et al. also reported on a convolutional neural network (CNN)-based model for robust, automatic contour propagation in prostate cancer for online adaptive proton therapy (202).

Relating to intra-fractional motion management, many studies have been published which apply deep machine learning towards challenges of real-time target tracking for both charged particles as well as photons. For example, Hirai et al. introduced a CNN-based model for marker-less real-time tumor tracking which was tested retrospectively on lung and liver cancer patients who received fluoroscopic imaging during carbon ion therapy (203). Mylonas et al. reported on the use of another CNN-based architecture for real-time tracking of arbitrarily shaped fiducial markers in fluoroscopy images (204). The motivation behind this study was to allow for fiducial marker segmentation without the need for prior maker-characterization, sparing the patient of additional imaging dose. Zhao et al. proposed a deep learning-based method for pancreatic tumor localization without the use of fiducial markers (205). Kim et al. introduced a CNN-based deep learning model for predict future motion of proton therapy patients based on facial expressions (206). In another promising study, Lin et al. describe a "super-learner" model which combined traditional neural networks with decision tree-based ML algorithms to predict the range of patient thoracic motion during proton therapy based on initial diagnostic CT and EMR data (207).

A substantial roadblock to implementing deep learning models in the clinical workflow stems from issues relating to model interpretability. Specifically, the inherent complexity of deep learning algorithms makes it difficult to understand how the models think (hence why DL models are often referred to as "black boxes") (208). Though capable of high accuracy predictions, DL models are still sensitive to unintended bias in the training data. The ability to understand and interpret the results of clinical models is critical for ensuring patient safety and quality of care in the event that such models fail (209). To this

end, the task of developing interpretable machine learning models without sacrificing model performance is an active research topic (210–212). One approach in handling the ethical question of what role a non-human entity should be trusted to play in clinical decision making is to require algorithms to follow a "human in the loop" framework. In a human-in-the-loop framework, clinicians remain fully integrated in the decision making process by allowing for human-computer interactions by which clinicians provide feedback/information to aid in model development, and the resulting models in turn provide accountable, interpretable decision support to the clinician (208).

SUMMARY

In this review, we provided an overview of the current clinical treatment methods for motion management in charged particle therapy as well as future emerging technologies and methodologies. As the use of charged particle therapy becomes more widespread and new treatment delivery modalities arise, further work will be necessary to ensure robust and accurate dose delivery. For the case of inter-fractional motion, further progress is also necessary to develop adaptive planning protocols which are triggered for clinically significant anatomical changes and can

be implemented within the time and resource constraints of a clinical setting. Another important task in this field is to continue the development of imaging and tracking systems which allow for accurate localization of the tumor and internal anatomy delivery at the treatment couch prior to delivery and in real time. One limitation of most studies on motion mitigation methods is that dosimetry is used the primary evaluation metric. Future studies which can connect motion mitigation methods to clinical outcomes would aid in accelerating standardization of care.

AUTHOR CONTRIBUTIONS

JP and WZ drafted the manuscript. AK, LD, and AR contributed with discussions, coordination, and critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

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