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Review Article

Particle arc therapy: Status and potential

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Abbreviations: 4DDD, 4-Dimensional Dose Deformation; BDT, Beam Delivery Time; DECT, Dual Energy Computed Tomography; DOF, Degrees of Freedom; ELF, Energy Layer Filtration; ELR, Energy Layer Reduction; ELST, Energy Layer Switching Time; GTV, Gross Tumor Volume; IMPT, Intensity Modulated Particle Therapy; IMRT, Intensity Modulated Radiation Therapy; LET, Linear Energy Transfer; MCO, Multi-criteria Optimization; MEE, Multi-energy Extraction; MFO, Multi-field Optimization; MIT, Multi-ion Therapy; NTCP, Normal Tissue Complication Probability; OAR, Organ-at-risk; PAT, Particle Arc Therapy; $PAT_{dynamic}$, Particle Arc Therapy using dynamic delivery; $PAT_{step\text{-}and\text{-}shoot}$, Particle Arc Therapy using step-and-shoot delivery; PBS, Pencil Beam Scanning; PMAT, Proton Mono-energetic Arc Therapy; PPS, Patient Positioning System; QA, Quality Assurance; RBE, Relative Biological Effectiveness; SBRT, Stereotactic Body Radiation Therapy; SEE, Single-energy Extraction; SFO, Single Field Optimization; SFUD, Single Field Uniform Dose; SHArc, Spot-scanning Hadron Arc; SPArc, Spot-scanning Proton Arc; SRS, Stereotactic Radio-surgery; TCP, Tumor Control Probability; TDS, Treatment Delivery System; TPS, Treatment Planning System; VMAT, Volumetric Modulated Arc Therapy.

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A B S T R A C T

There is a rising interest in developing and utilizing arc delivery techniques with charged particle beams, e.g., proton, carbon or other ions, for clinical implementation. In this work, perspectives from the European Society for Radiotherapy and Oncology (ESTRO) 2022 physics workshop on *particle arc therapy* are reported. This outlook provides an outline and prospective vision for the path forward to clinically deliverable proton, carbon, and other ion arc treatments. Through the collaboration among industry, academic, and clinical research and development, the scientific landscape and outlook for particle arc therapy are presented here to help our community understand the physics, radiobiology, and clinical principles. The work is presented in three main sections: (i) treatment planning, (ii) treatment delivery, and (iii) clinical outlook.

Introduction

The global accessibility of particle therapy[1] using protons and carbon ions is rising, offering high-precision radiotherapy treatments to more patients each year [1]. Current clinical practice involves a delivery technique called pencil beam scanning (PBS), where a narrow ion beam, or 'pencil beam', is magnetically focused and steered to deliver precise radiation doses by scanning across the tumor in a predefined pattern, with changes in beam energy to pin-point different depths within the tumor. There are different variations of PBS, including spot scanning that delivers the radiation in discrete spots with the beam off between spots, raster scanning that delivers spots with the beam on between spots, and line scanning that irradiates in a continuous scanning line with the beam on continuously. PBS delivery requires intensity modulated particle therapy (IMPT) planning techniques, which use an inverse planning algorithm to optimize the dose distribution by modulating the fluence of pencil beams within each field. The last decade has seen an increased interest in developing and translating advanced ion beam delivery techniques [2,3], from the conventional treatment settings and conditions to ultra-high dose-rate (uHDR), spatially fractionated treatment regimens, multi-modality treatments and from "static" step-and-shoot to dynamic deliveries such as *particle arc therapy* (PAT).

PAT is an advanced IMPT treatment technology that delivers highly precise, conformal radiation doses to tumors by rotating the beam around the patient, either using a dynamic or step-and-shoot delivery.[2] Initially, the particle arc concept may seem somewhat counter-intuitive to the main principles of particle therapy, where the treatment delivery can be performed with a single or few beams, minimizing the patient's integral dose and/or irradiated volume. Additionally, it proposes the use of a dynamic rotational gantry with hundreds of tons while achieving submillimeter accuracy — which is a considerable feat of engineering (Fig. 1). Despite these known challenges, the concept of PAT is not particularly new. First proposed in 1995 by Deasy *et al.*, proton arc therapy was investigated in the context of distal edge tracking (DET) tomotherapy [4] and by Bortfeld in studying the capabilities and limits of dose conformity of charged particle beams using rotational therapy [5]. Investigations using passive-scattering systems and step-and-shoot experiments and simulated delivery, such as Sandison *et al.* and Seco *et al.,* demonstrated the potential advantages of proton arc irradiation for chestwall treatments and lung stereotactic body radiation therapy (SBRT) [6,7]. Proton mono-energetic arc therapy (PMAT) was introduced by Carabe *et al.,* detailing the first efficient arc delivery approach using scanning technology [8,9]. More recently, Spot-scanning Proton Arc (SPArc) therapy via the optimization of hundreds of energy layers and thousands of spots across the arc trajectories was introduced by Ding *et al.* [10], demonstrating both robust and efficient delivery with the first prototype proton arc therapy system using a clinical machine [11]. Since then, numerous works have been published detailing dosimetric advantages for several disease sites and potential delivery efficiency improvements using proton arc compared to IMPT where a limited number of static beam angles is utilized (hereafter referred to simply as 'IMPT' for conciseness). Similarly, spot-scanning hadron arc (SHArc) therapy with heavier ions, i.e., PAT using helium, carbon, oxygen or neon ions (also referred to as ion arcs), was proposed by Mein *et al.*, demonstrating its potential for enhancement of linear energy transfer (LET[3]) in the gross tumor volume (GTV) for combatting radioresistant disease [12].

A majority of photon radiotherapy for curative intent now uses rotational intensity modulated therapy (IMRT) and goes under a variety of names, including volume modulated arc therapy (VMAT) and helical tomotherapy. Several photon rotational therapy systems have been developed to support VMAT [13–15], providing efficient delivery and streamlining image-guided treatment techniques [16]. One of the biggest challenges for PAT is that the continuous arc delivery with gantry-based systems was hampered by several technical hurdles, such as the small but significant gantry sag, and angularly dependent magnetic field changes, which require continuous beam steering. Despite these challenges, different vendors and collaborating institutions are working to push the technology towards the clinical product. With the recent development of novel planning optimization algorithms, new delivery mechanisms, and the compact size proton gantry, such a concept has been demonstrated in a clinical proton system, which is considered as a major milestone towards the clinical implementation [11]. Additionally, with the revival of chair treatments within particle therapy, PAT could potentially be realizable at a lower cost (Fig. 1). With the existing preliminary investigation and publications, the potential benefits of arc delivery with charged particle beams have been shown to include improved delivery workflow, decreased delivery time, plan quality/conformality improvements, increased robustness, and enhanced biophysical distributions. Nonetheless, several developmental challenges and unknowns for PAT delivery must be addressed prior to safe, efficient, and effective treatment.

In this work, an outline of the ESTRO 2022 physics workshop on PAT is reported. This outlook provides an overview of the status of PAT and a prospective vision for the path forward to clinically deliverable proton and other ion arc treatments using scanning delivery technology. Through the collaboration among industry, academic, and clinical research and development, the scientific landscape and outlook for PAT delivery methods (including both $PAT_{dynamic}$ and $PAT_{step\text{-}and\text{-}shoot}$) using

[1] Charged particle therapy, also known as ion beam therapy or hadron therapy, is a form of external beam radiotherapy using accelerated beams of positively charged ions for cancer treatment, e.g. protons, and other ions such as carbon.

[2] Dynamic Arc ($PAT_{dynamic}$): A treatment delivery technique, system or treatment plan that enables continuous irradiation within the arc, e.g., scanning the spot and/or switching the energy layers, while the gantry or PPS is dynamically rotating.Step-and-shoot Arc ($PAT_{step\text{-}and\text{-}shoot}$): A treatment delivery technique, system or treatment plan that enables irradiation of each treatment direction within the arc while the gantry or PPS is fully stopped (also referred to as discrete arc).

[3] LET is a quantity to describe the radiation quality of ion beams and is defined as the amount of energy that a particle transfers per unit track length as it travels through a medium (units: keV/μm). LET increases with decreasing velocity and directly influences the physical dose distribution and biological effectiveness of the particle radiation. Due to the mixed-radiation field generated in ion-beam therapy, dose-averaged LET (LET_d) or related quantifications are used in reporting. For more information, please refer to a recent systematic review on the usage of averaged LET in particle therapy [207].

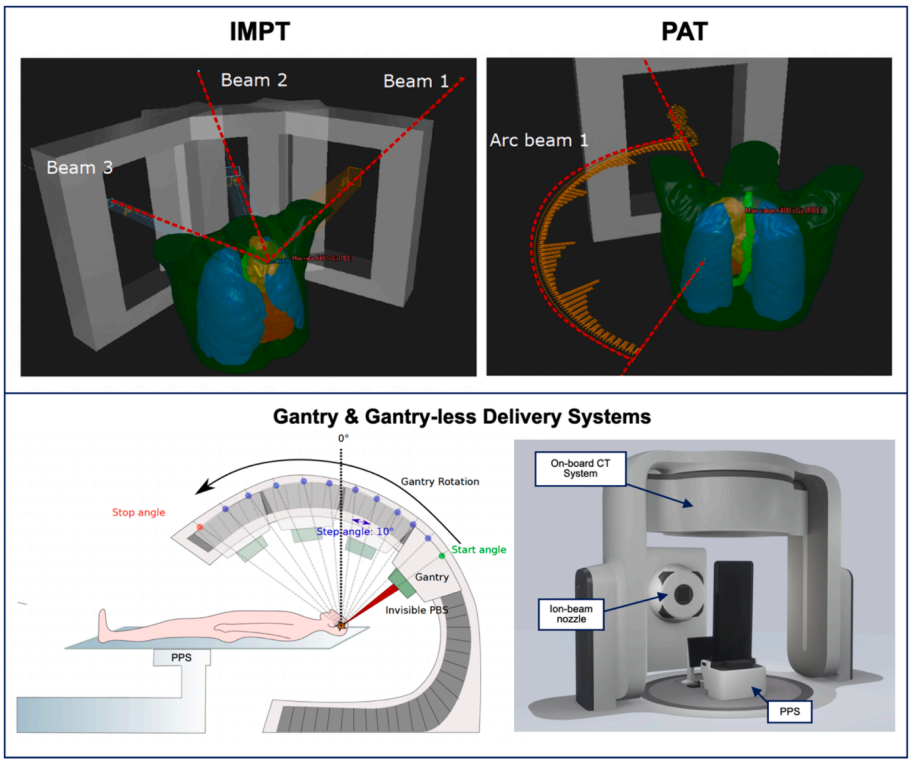

Fig. 1. IMPT versus particle arc therapy (PAT) planning and delivery techniques. PAT involves rotational motion of a gantry and/or patient position system (PPS) using protons, carbon and/or novel ion beams, e.g., spot-scanning proton and hadron arc therapy [12,17]. PAT treatments can be delivered dynamically (continuous rotation while beam-on) or step-and-shoot (beam-on only at discrete irradiation directions). Examples for gantry and gantry-less (upright PPS) delivery systems for PAT are depicted
adapted from [18].

PBS technology is presented. Arc delivery using passive scattering delivery technology is out of the scope of this work. The work is presented in three main sections: (i) treatment planning, (ii) treatment delivery, and (iii) clinical outlook.

1. Treatment planning and optimization

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In radiotherapy, a treatment planning system (TPS) plays a major role in generating an optimal treatment plan to accurately deliver radiation doses to tumors while sparing surrounding healthy tissues, ensuring both treatment efficacy and patient safety. IMPT treatment plans can be optimized and delivered using two different methodologies: single-field optimization (SFO), also referred to as single field uniform dose (SFUD), where each field is optimized to cover the target uniformly, and multi-field optimization (MFO), where the dose distribution from multiple fields is optimized simultaneously to achieve a homogenous dose within the target and minimize the dose to surrounding healthy tissues [19]. There are case-specific benefits and trade-offs of using SFO or MFO techniques as outlined in previous reports [20,21].

With accurate and robust dose calculation and robust optimization for ion beams available in clinical systems, current research and development efforts are focusing beyond calculation accuracy, expanding towards further increasing the therapeutic window with new treatment planning and delivery strategies such as PAT. Other efforts aim to reduce treatment margins enabled by more advanced imaging techniques and elaborate adaptive workflows, as well as radio-biological considerations [22]. Increasing daily patient treatment throughput in the clinic, delivery efficiency and optimization time are also of high importance [16]. Although PAT might sound similar to VMAT for photons, the two techniques are dramatically different in the accelerator system, beamline configuration, irradiation and scanning sequences, and mechanical limitations of the gantry and couch. Thus, experience and knowledge from VMAT treatment planning and optimization might not be directly applicable to PAT. To address technical challenges associated with the development and clinical implementation of PAT, various delivery and planning methods have been introduced to facilitate the translation of efficient and robust PAT. The differences between the methods are mainly linked to the stage of engineering and technological advancements of particle therapy systems at the time. Examples from the last decades include facility transition from double scattering to scanned delivery [23,24], distal edge tracking methods for improving target conformity [4] and mono-energetic arc to improve efficiency by eliminating the need for prolonged energy layer switching time (ELST) [25,26]. In general, PAT planning and optimization will require dedicated MFO techniques to generate high-quality deliverable treatments. Prior to clinical integration, PAT systems must address four major aspects of planning: (1) the delivery time (2) the plan quality, such as dose and robustness, (3) the computing efficiency, and (4) LET_d and relative biological effectiveness (RBE)[4] distributions (Fig. 2.a). These can be

[4] The Relative Biological Effectiveness (RBE) is a measure comparing the biological effectiveness of ionizing radiation types to photons, defined by the equation $RBE = \frac{D_x}{D_{particle}}$, where D_x and D_p are the photon and particle radiation doses, respectively, needed to achieve the same effect [208]. RBE is a unit-less quantity that, in practice, is applied during to convert physical dose to effective (or biological) dose, i.e., $D_{RBE} = RBE \times D_{physical}$. Refer to the IAEA-ICRU joint report (TRS-461) for further information [62].

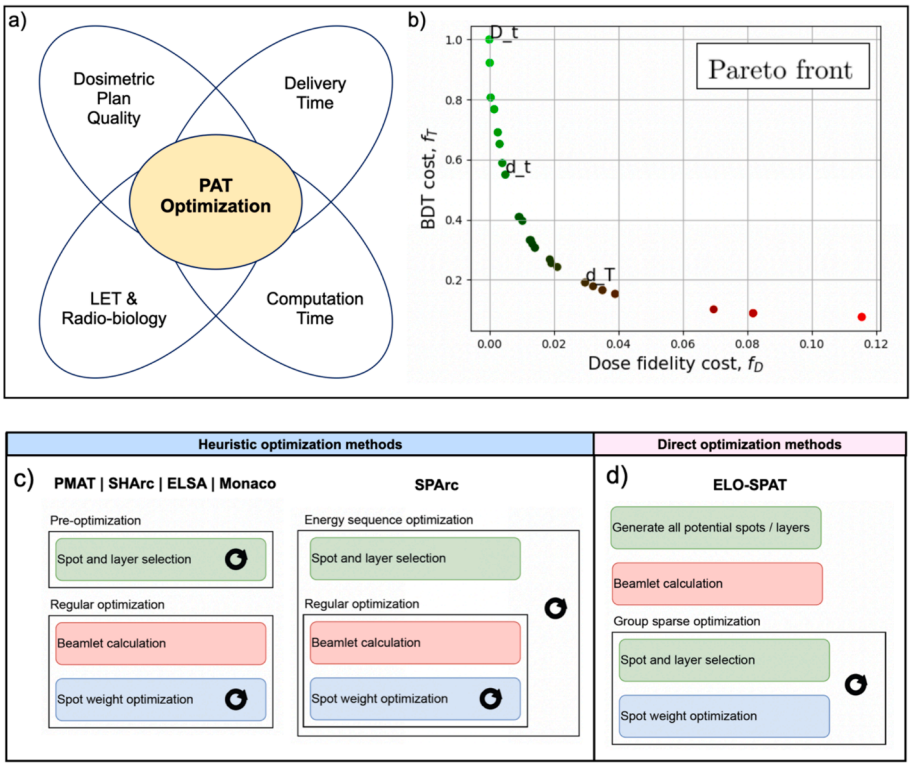

Fig. 2. (a) Balancing optimization goals of plan quality, computational time, delivery efficiency and LET/radio-biological considerations is a key challenge in PAT algorithm development. (b) Example pareto surface during MCO for PAT, where red points represent optimizations with more weighting placed on the dose fidelity term while the green points represent optimization with more weighting placed on the delivery time objective [49]. Algorithm and workflow for proposed approaches to PAT treatment planning and optimization, i.e., (c) heuristic (SPArc, PMAT, SHArc, ELSA, and Monaco) and d) direct (ELO-SPAT) [8,10,12,33,36,38]). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.
adapted from [18].

achieved by evaluating and refining optimization methods for PAT.

PAT trajectory selection and plan design

With the advent of scanning technology, particle therapy has become highly degenerate compared to passively scattered delivery techniques. In other words, PBS can irradiate similar treatments using different dose delivery patterns and field arrangements by optimizing beam angles, spot position and spot intensity, i.e., monitor units (MUs) per spot. The addition of arc delivery with PBS as opposed to a limited number of static beams has the potential to greatly increase the degrees of freedom in treatment design and optimization. Characteristics of the particle arc treatment may depend on various factors such as the treatment site, specifics of the clinical scenario, machine capabilities and facility preference. In terms of the appropriate selection of arc parameters, arc trajectories may involve *full*, *partial* or *multiple arcs* if needed. For non-centrally located tumors there is an opportunity to use partial arcs that traverse only from the closest directions, thereby minimizing the integral dose to normal tissue while still providing optimal tumor coverage. For more centrally located tumors, full arc treatments may be more ideal in order to lower the dose to neighboring critical structures but there may be immunological or other benefits with having regions of negligible dose neighboring the tumor. Arc trajectory considerations do not only depend on the location of the tumor but also the location of OARs. Partial arcs could be beneficial to avoid fields passing through OARs and/or body parts (e.g., shoulders) or fixation and support devices (e.g., couch borders) that could affect robustness. In other words, the extent of the arc trajectory may not be solely dependent on geometric and/or prescription considerations of the tumor location and reduction of the low-dose bath to normal tissue. Ultimately, PAT offers numerous degrees of freedom in the plan quality modulation. Attributes for a set of arc trajectories in a given treatment will be highly dependent on the disease sites and clinical needs.

Optimization for treatment efficiency

Treatment efficiency plays a key role in the treatment plan generation process. Radiotherapy setup including image verification time constitutes about half of a patient's time in a particle therapy treatment room [27]. The treatment delivery accounts for most of the remaining time and effectively determines a particle therapy center's daily treatment throughput, as well as the plan quality since the degree of freedom is directly associated with the number of spots, energy layers, and gantry control points. There can be large variations in treatment delivery times between centers, since different machine-specific irradiation sequences[5] may result in different treatment delivery times for similar plans. For example, synchrotron and cyclotron-based accelerators have different characteristics influencing the delivery time. Furthermore, a system with a rotating chair and a fixed beamline may pose other challenges than a gantry-based solution (see section 2 on gantry and gantry-less systems).

An important example of a delivery constraint is the duration of switching the energy layer. Several commonly used cyclotron- and synchrotron-based systems for particle therapy can, in fact, suffer from a substantially longer time for upward than downward switches in beam

[5] A "sequence" in particle therapy refers to the (machine-specific) order and method of delivering the ion beam. "Sequencing" refers to the process of determining the optimal order and timing for delivering the radiation doses during treatment, including beam angles, energy layers, and scanned beam position (e.g., spots) within those layers.

energy. The treatment planning process in general, and more specifically, the optimization algorithms for PAT, must take these machine-specific characteristics into account. The actual delivery time is a dynamic process that includes mechanical parameters, such as maximum gantry (or chair) rotation velocity, acceleration, deceleration, and jerk constraints, in addition to irradiation parameters [28]. Optimizing a particle arc to align with the actual delivery sequence and reducing delivery time is complex and requires time-consuming computations. As a consequence, directly optimizing the actual particle arc delivery time in conjunction with the dosimetric quantities still remains a mathematical challenge. As an alternative, appropriate surrogates of the treatment delivery time for a given system can be more easily incorporated into the treatment plan optimization. As described in the next section, many efforts have been directed towards reducing delivery time through energy layer sequencing (from high to low), as well as through spot and energy layer reduction. Some approaches have been proven to constitute reasonable heuristics for reducing delivery time for certain machines. Spot reduction could be an effective optimization approach to potentially increase delivery efficiency as scanning numerous spots takes significant time [29–31]. Recent studies have demonstrated that the reduced delivery times afforded by spot reduction could enable increased use of rescanning for motion mitigation (see section 3 on motion management) [32].

Though the mechanical behavior and mechanism of rotational arc therapy are still unclear, with the development of prototype TDS (see section 2), the scientific community can precisely model the particle arc treatment delivery mechanism and understand the arc irradiation sequence and mechanical limitations [11]. These models and information can provide our community with ground truth and reference to guide future TPS development.

PAT optimization approaches

Two main types of optimization approaches are under investigation for PAT optimization: *heuristic* and *direct* optimization approaches.

In the *heuristic* optimization method, optimization techniques typically start with a pre-selection of energy layers and spots. Then, the algorithm continues the optimization of plan quality or searches for energy layer and spots distributions, sequentially or iteratively [10,30]. In the *direct* optimization methods, the optimization aims to minimize the cost function directly, e.g., the cost plan quality and delivery time objectives together. Normally a large number of candidate energy layers and spots are assigned to each discretized control point, and the selection of energy layers and spots is made as part of the optimization process, steered by planning objectives [33–35]. A concept diagram for existing optimization approaches is provided in Fig. 2. In general, *heuristic* optimization methods solve major obstacles in the arc plan design and execution, such as memory usage, computation burdens and compatibility with different optimization objectives. *Direct* optimization approaches, on the other hand, are substantially more computationally heavy, but include more degrees of freedom in designing an optimal plan.

The first and most studied heuristic optimization methods to-date are based on the SPArc algorithm which is based on the iterative optimization of multiple modules, e.g., the dose, energy layer, spot selection, and delivery sequencing (*heuristic-iterative approach*) [10]. SPArc begins with a pre-selection of energy layers and spot placement, using a large number of IMPT fields (dozens) spanning the arc as the initial input. In a subsequent step, the algorithm resamples, optimizes, selects, filters, and adjusts the energy layer number, spot number, and weighting across the control points iteratively based on the sequencing of treatment delivery, e.g., energy layers, spots or other user criteria. This optimization platform has been shown to achieve clinically feasible and reasonable solutions in terms of delivery time, dosimetric quality, and robustness and has been tested in a broad range of patient geometries and clinical indications, demonstrating the potential clinical benefits of PAT (see section 3 on clinical outlook). Other *heuristic* approaches through two-sequential steps via pre-selection and spot-weight optimization (*heuristic-sequential approach)* have been implemented in commercial products such as RayStation [36,37] and Monaco [38,39]. In contrast to the SPArc algorithm, the spot and energy layer selection for those systems is directly performed per discretized direction prior to optimization. Energy layer sequencing is thus considered from the beginning in the pre-selection step by finding a suitable arc trajectory based on geometrical and other considerations. In the following spot-weight optimization stage, the weights of the pre-selected spots are altered to meet the optimization objectives. In this process, low-weighted spots and energy layers can be filtered out in order to meet machine delivery constraints and speed up delivery. The major advantage of using such a pre-selection approach is that it substantially reduces plan optimization time as it has fewer energy layers before the spot-weight optimization, which in turn could allow for the user to run several optimization rounds to tune plan parameters and optimization objectives to meet the clinical goals of the treatment [37,38,40]. A main disadvantage is that the solution space can be limited from the start as compared to *direct* or other *heuristic* optimization approaches. For heuristic-iterative methods, such as the SPArc algorithm, further challenges might arise due to the prolonged optimization time related to the numerous iterations needed to reach a clinical solution such as plan quality, delivery efficiency and accuracy, while the advantage is that it could be applied and adjusted to fit any clinical scenario and for varieties of particle therapy systems by integration with different selection criteria or modules through the iterative approach. Other heuristic approaches for proton arc therapy were also investigated [36,41–44]. For heavier ions like helium, carbon, oxygen and neon ions, the SHArc optimization framework is the main example of *heuristic* methods [45].

Direct optimization approaches, combining spot weight and energy sequence optimization in a single step, has also been proposed to solve the PAT optimization challenge depicted in Fig. 2. As the true beam delivery time (BDT) is machine-specific and could result in a very complex formula, a surrogate or a simplified BDT model is desirable to formulate PAT as a rigorous mathematical optimization problem. One of the first representative works on energy layer optimization for spot-scanning proton arc therapy (ELO-SPAT) is detailed in Gu *et al.* [33], where a regularization term was added in the objective function to increase energy layer sparsity among the gantry angles and promote a time-efficient ordering of the energy layers in the solution. This idea was further investigated by Zhang *et al.* [46], who enhanced the optimization by accelerating processing speed and improving both delivery efficiency and plan quality using a so-called energy matrix regularization. Recently, an algorithm based on iterative convex relaxation was devised to directly minimize the number of energy jumps, showing improved delivery efficiency compared to the previous method [47].

Despite the higher degrees of freedom in direct optimization methods, several drawbacks arise. First, the conventional spot-weight optimizer is rendered inapplicable due to adding regularization terms to the objective function, which makes it non-convex (i.e., multiple local minima) or non-smooth (i.e., non-differentiable terms). Furthermore, each new penalty term introduces a weighting parameter requiring tuning. While efforts have been made to improve optimization efficiency using the aforementioned solvers, run times for these algorithms remain substantial. A qualitative study comparing optimization problem statements and their corresponding solvers for particle arc therapy demonstrates that energy sequencing poses significant mathematical challenges, suggesting that global optimization methods are not particularly well-suited for this context [35]. Nonetheless, the concepts and approaches from these studies may still hold value and should be taken into consideration in specific scenarios. While most of the research on PAT optimization focuses on energy layer sparsity and sequencing to minimize the delivery time for gantry-based cyclotron (or synchrocyclotron) systems, a study demonstrated that spot-scanning time can be a contributor to the delivery time, especially for systems without line

scanning techniques, and direct spot sparsity optimization techniques were subsequently developed [48]. Multi-criteria optimization (MCO) with a surrogate or even the true machine delivery sequence model would also be an effective way to address trade-offs between plan quality and delivery time, and, eventually, let the clinical users select the optimal decision from a Pareto surface [49] (Fig. 2). Other works design innovative stochastic algorithms, e.g., Dynamically collimated proton Arc (DNA) genetic optimization, for spot-scanning proton therapy for delivery systems that make use of a multi-leaf collimator [50] further demonstrating both improvements in target conformity and need for complex problems solvers for efficient arc optimization and delivery.

A recent thesis by Wuyckens (2024) thoroughly outlines, developments and investigates viability of different approaches to PAT optimization, demonstrating that designing PAT plan using algorithmic methods is an NP-hard problem [18,51]. NP-hard refers to a class of problems that are at least as hard as the hardest problems in NP (nondeterministic polynomial time), meaning that no known algorithm can solve all NP-hard problems efficiently, i.e., in polynomial time for all cases. The complexity is rooted in the energy sequencing constraint, further highlighting the major challenges and needs for efficient PAT algorithms and heuristics to navigate the complexities effectively. Wuyckens states that "NP-hardness of the proton arc problem should not discourage further research in this area. it should serve as a catalyst for the development of heuristic approaches and approximation algorithms that can provide near-optimal solutions within acceptable time frames.".

Optimization for plan quality and robustness

Robustness is a key feature in IMPT and, consequently should be applied during PAT planning and optimization. Achieving a certain level of robustness in the dose distribution (e,g., considering ion beam range and patient positioning uncertainty) may be more challenging in PAT, due to interlaced spot maps from a multitude of directions, compared to IMPT with a set of stacked energy layers from a few directions. Since 2016, robust optimization has been an integral part of PAT optimization approaches [36,52,53]. Although works have indicated that robustly optimized proton arc treatment plans may be more robust in the presence of setup error, range uncertainties, geometry changes and mobile target interplay effect compared to IMPT plans [54,55], extensive additional studies are warranted in this area, especially for ion beams which require variable RBE models (helium, carbon, etc.) discussed in the following sections. Moreover, the dosimetric impact of changes in the daily patient's geometry remains to be thoroughly investigated, especially in H&N cancer patients. Recently, some studies reported that PAT plans could be more sensitive to inter-fractional changes than IMPT plans in these patient populations [44,56,57]. Findings along this direction show the necessity to assess the robustness of the treatment plan throughout the treatment course, and robustness evaluation tools should be included in treatment planning systems for PAT. Challenges with inter-fractional robustness in PAT could also lead to a higher need for adaptive radiotherapy than in conventional planning (see section 3 on motion management and adaptive therapy). Given longer calculation and optimization times compared to IMPT, further work is needed to improve fast online PAT re-optimization for compatibility with adaptive therapy.

Optimization for LET and RBE

Aside from the promises of high dose conformity, proton arc therapy has demonstrated its effectiveness in the LET modulation, as initially demonstrated by PMAT [8]. With PMAT it is possible to achieve an efficient delivery in combination with increased LET in the target, and may be more importantly avoiding high LET in normal sensitive tissues, by utilizing a single energy layer which stops in the central parts of the tumor. Two of the main challenges that remain to be verified using PMAT are the plan dosimetric/LET robustness and compatibility with various diseases and patient geometry. In general, the additional degrees of freedom of PAT are well suited to be combined with LET optimization, which could lead to a new era of biologically driven treatment design (Fig. 3). LET optimization for proton arc plans has also been demonstrated using the SPArc approach [58].

Recent works introduce PAT with other ion species, i.e., SHArc therapy using helium, carbon, oxygen and/or neon ions, demonstrating highly conformal dose distributions and high-LET boosting on the order of ~ 100–200 keV/μm inside the target, which has not been seen previously with other delivery methods (Fig. 3) [12,53,59]. The ability to escalate LET has the potential to overcome hypoxia and could be a game changer in the management of radio-resistant tumors [12,60] (see section 3 on radiobiology). Exploring the use of ion treatments using helium, carbon, oxygen and neon ions is still in the early stages and in practice, and given current systems, SHArc delivery would be subject to the synchrotron spill structure with distinct extraction and acceleration phases, with each spill cycle lasting up to several seconds (see section 2 on delivery). Fig. 3 provides examples of IMPT versus PAT using protons and carbon ions, demonstrating the increased degrees of freedom to redistribute LET_d.

For proton therapy, physical dose optimization is performed and distributions are converted to effective dose by simply scaling uniformly by a factor of 1.1. Different phenomenological and mechanistic models are available in the literature to investigate variable RBE for proton therapy [61] and can be used to predict effective dose; however, these models are not applied clinically due to several considerations as discussed in AAPM TG-256 (see section 3 on LET & RBE). The controversy with using a constant RBE of 1.1 is that end-of-range, underestimations in the biological effect may lead to unexpected toxicity in OARs. With respect to LET_d optimization, PAT potentially affords more degrees of freedom in re-distributing LET_d to avoid unexpected toxicity while still applying a constant RBE. For heavier ions, e.g. helium and carbon, it is necessary to apply variable RBE models in the biological dose calculation, as described in IAEA TRS-461 [62], which further increases optimization complexity and computational demand, considerably more-so compared to proton therapy using constant RBE of 1.1 [63,64]. When treatment planning applies variable RBE models, biological dose calculation and optimization is performed which must model and account for the changes in the mixed radiation field in the entrance channel, Bragg peak and the fragmentation tail, by handling large databases and complex routines (i.e., ion species dependent interactions, nuclear reactions, etc.). Consequently, MFO techniques are more commonly applied in carbon ion therapy due to the added degrees of freedom as opposed to SFO. Furthermore, the RBE is determined from this mixed radiation field via the use of mechanistic models, further increasing computational needs within the dose calculation and optimization algorithms [65–67]. This presents additional challenges and opportunities in forming optimization strategies for arc and thus, robust optimization may be essential for PAT delivery with heavier ions to ensure dosimetric accuracy and mitigate the impact of strong LET/RBE gradients on uncertainties. Recent works have addressed the reduction of physical and biological uncertainties with multi-ion delivery, i.e., mixing lower and higher-LET ion beams in a single fraction [68–70]. Nevertheless, the ability to escalate LET and its impact on improving radio-biological robustness calls for further exploration. For PAT optimization, these challenges may need to be specifically addressed in developing algorithms to further improve planning efficiency.

Commercial solutions and standardization to support PAT

Broader clinical implementations of emerging treatment techniques rely on support and adoption by industry partners. Today, two proton TPS vendors, RaySearch Laboratories (RayStation) and Elekta (Monaco), support proton arc planning modules with robust dose and LET-based optimization and Monte Carlo on GPU for fast and accurate dose calculation. The implementation of PAT in the clinical TPS allows more

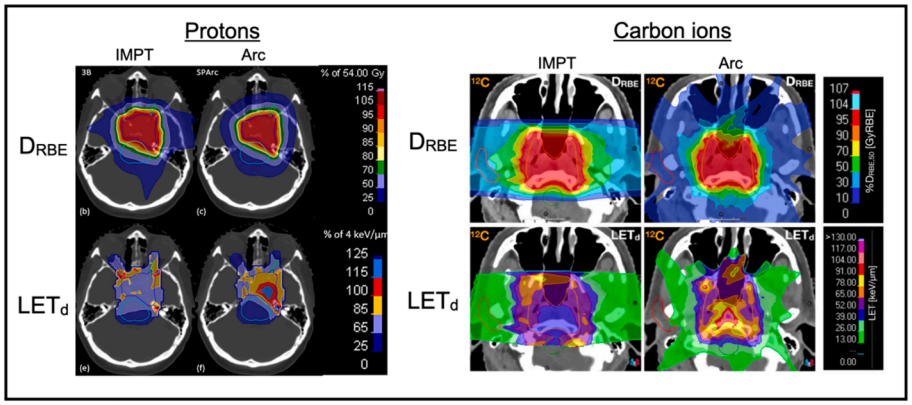

Fig. 3. Dose and dose-weighted linear energy transfer (LET_d) distributions for IMPT versus PAT algorithms in brain cases using protons and carbon ions [53,58].

users to access PAT and exploit its potential clinical benefit. In the near future, full integration of clinical workflows and platforms will drive an efficient, safe, and precise implementation of PAT for a wide range of clinical indications. In particular, consensus is needed in defining the DICOM file formats and information standards for PAT such as control point, delivery window, gantry rotation, couch motion, snout reposition, beam/spill request, energy layer switching, and spot MUs. These updates are essential for cross-system compatibility and will require collaboration and agreements between multiple vendors and communities. These information standards and system modifications will involve but are not limited to the TPS, oncology information system (OIS) and particle therapy TDS.

2. Treatment delivery

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Status

Particle arc delivery involves the rotational motion of either the patient, the beam delivery system, or a combination of both. In general, PAT plans can be delivered in two different delivery modes: *dynamic* and/or *step-and-shoot* (Fig. 1). To deliver $PAT_{dynamic}$, e.g., continuous rotation of the gantry or PPS, plan generation may require optimization strategies taking into account machine-specific delivery characteristics, such as mechanical limitations, specifics of the energy layer selection and switching systems, spot irradiation sequences and scanning time. On the other hand, $PAT_{step\text{-}and\text{-}shoot}$ plans, e.g, discrete arc [57,71,72], do not need to explicitly consider a dynamic machine delivery sequence or mechanical limitation. Instead, energy layer and spot number reduction are needed to ensure an efficient delivery [73,74].

The first demonstrations of proton arc delivery took place in the 1990′s and employed step-and-shoot using passive scattering technology to investigate the treatment of the chest wall in place of electron therapy [6]. In 2013, step-and-shoot delivery simulation for both passive scattering and IMPT was investigated in the context of SBRT [7]. Despite promising results from prior studies [26,75–77], the efficiency and robustness of the proposed optimization and delivery techniques for rotational proton therapy were limited and hindered by the available technology at the time.

More recently, in 2018, the first efficient and robust $PAT_{dynamic}$ using PBS was demonstrated [11]. This work marks a milestone towards clinical feasibility and translation of proton arc therapy. The delivery process for proton arc therapy is highly complex and requires dedicated technology to establish a beam delivery system with a higher level of stability than many currently operating facilities and accurate synchronization of spot delivery patterns with gantry motion. The type of gantry and its weight/size play a major role in determining how a facility may go about developing and implementing PAT. Many facilities still operate with traditional, larger-sized proton gantries with dimensions of ~ 8–12 m and masses of 200 tons or more. The first SPArc prototype delivery, however, was performed using a compact clinical proton gantry (~75 tons), achieving both clinical efficiency and submillimeter delivery accuracy. The older and larger gantry systems may pose additional challenges in dynamically maintaining isocentricity and synchronization of beam delivery with rotation; however, dedicated investigations are still needed to determine these exact technical limitations for arc delivery.

An alternative economical approach to PAT does not involve a gantry system and instead proposes a fixed beam line with a rotational chair or upright PPS. This eliminates the need to change gantry magnet parameters for $PAT_{dynamic}$ and arc angular velocity can be modulated without large gantry inertias. Recent reviews explore the economic and clinical reasons for upright patient positioning system (PPS), assess existing/future designs, and offer recommendations for system implementation [78]. These more affordable rotational technologies are currently under development by industry (e.g., Leo cancer care and P-cure) and could help streamline the development and clinical accessibility of particle therapy at large [57,79]. There are, however, several remaining challenges related to upright patient postures, which need to be addressed before they can enter routine clinical usage.

Opportunities and challenges

A major bottleneck in an efficient arc delivery is the current state of clinical scanning nozzle and beamline technology, which for many systems involves relatively slow ELST on the order of seconds from high to low energies and even longer from low to high energies due to magnetic hysteresis. Additionally, it is understood that robust arc plans may require a greater number of spots and energies per plan, which further prolong the treatment time. These limitations could stunt the full exploitation of delivery efficiency if not addressed in next-phase development efforts for PAT. Hence, improving ELST and spot/raster-scanning speed is a crucial area for future development. Additionally, different beam delivery systems may have distinct delivery sequences, including differences in dose rate, spot switching time, and ELST. These differences should be considered in the treatment planning process to fully utilize the delivery efficiency of PAT.

Aside from beam delivery characteristics, dedicated safety systems for gantry collision during arc delivery are needed since many current systems do not have robust mechanisms for collision prevention. Novel collision detection systems or gantries with increased clearance should be considered to address this concern. The integration of surface

guidance technology in particle therapy could offer a streamlined approach for real-time patient monitoring during delivery, particularly useful for PAT to enhance motion management, enable gating techniques, and improve collision detection to ensure patient safety, as discussed in AAPM TG-302 [80].

Continued research and development in these areas have the potential to further advance PAT, leading to improved treatment outcomes and more efficient delivery techniques for cancer patients. In the following sub-sections, the status, challenges, and considerations for the development of particle arc delivery systems are explored in terms of gantry-based and gantry-less systems, machine delivery sequencing and modeling, accelerator systems, dosimetry, and quality assurance (QA).

Optimizing accelerator systems and modeling machine-specific delivery sequence and delivery time

The accelerator type (e.g., cyclotron, synchrotron or synchrocyclotron) and delivery system model play an important role in defining the beam delivery characteristics (Fig. 4). Scanned ion beam therapy involves optimizing and delivering a sequence of spots, number of particles per spot, and energy layers and the sequence of energy layers and scanning path is determined by machine parameters and facility preferences. IMPT does not typically consider a temporal aspect of delivery with the use of fixed beam angles. However, in practice, the energy sequence and scanning path optimization are performed to ensure safe irradiation and reduce uncertainties in dose delivery. The final sequence will depend on the accelerator type and delivery technique (e.g., spot, raster or line scanning). For $PAT_{dynamic}$, determining the exact sequence as a function of time and gantry angle becomes critical, analogous to control point and multi-leaf collimator sequences in VMAT planning and delivery. In other words, understanding a system's BDT and sequence prediction model will play an important role in the plan generation process for PAT. Here we listed the existing published particle therapy units and their own unique BDT model as follows:

- Hitachi's synchrotron-based proton system (ProbeatV5) uses discrete spot-scanning. A BDT model was generated for the ProbeatV5 with experimentally determined delivery parameters and was used to study novel multiple-energy extraction delivery techniques [81,82]. Raster scanning, referred as Dose Driven Continuous Scanning (DDCS) in the Hitachi system, was recently made available for proton delivery (previously only used for carbon ions) and a BDT model was simulated for the Hitachi Hybrid Particle Therapy System [83].
- For Ion Beam Application (IBA), there are two systems primarily used currently for proton therapy: the cyclotron based ProteusPLUS® multi-room machine and the compact superconducting synchrocyclotron (S2C2) based ProteusONE® single room machine. Dedicated BDT models were established for the IBA ProteusPLUS® at US/European-based facilities for standard delivery as well as volumetric and layer repainting techniques [84,85]. For the IBA ProteusONE®, a unique high intensity pulsed beam is extracted and delivers every spot in each energy layer through several radiation bursts and a dedicated BDT and sequence prediction model was recently developed [48].
- Mevion's PBS system includes a compact, gantry-mounted superconducting synchrocyclotron accelerator with a proton MLC and nozzle-mounted range modulator system for fast ELST of ~ 50 ms (Mevion S250i with Hyperscan and Adaptive Aperature™). A Mevion press release announced an ongoing partnership with Leo Cancer Care to develop the S250-FIT, a novel gantry-less PBS system using upright positioners (see section 2 on gantry-less delivery) designed to "support fast access to emerging technologies like arc therapy" [86]. There is currently no published machine-specific BDT model for Mevion systems.
- For other PT vendors/system types: At the time of writing this paper, machine-specific BDT and sequencing prediction models have yet to be published. These areas remain to be explored by the institutions independently and/or with the vendor's collaboration.

To be clear, cyclotron- and synchrotron-based systems (and, in turn, different system models) will require differences in the approach to PAT plan design and clinical implementation (Fig. 4.a). Fortunately, vendors have substantially increased delivery efficiency by reducing beam pauses between subsequent energy layers (ELST~50–200 ms) for cyclotron and synchrocyclotron proton therapy systems [73,87,88]. Treatment delivery times depend on several factors, including the duration of the energy-switching process, the amount of energy needed, and the scanning volume. Fast energy switching is important not just for increasing delivery efficiency but is also beneficial when treating moving tumors and implementing motion mitigation techniques in PBS, e.g., repainting. It is known that, to an extent, more energy layers in a PAT treatment plan increases degrees of freedom, enabling potentially improved target conformality (as discussed in section 1 on treatment planning and optimization). Rapid energy switching in PAT will afford both efficiency and flexibility in the complex energy sequencing needed for beam delivery during dynamic rotational motion. Roadmap publications on proton and helium ion therapy provide in-depth discussion of the status and directions of technological design and solutions for improving cost-effectiveness and delivery efficiency, which may be critical for PAT [89,90].

Most publications on proton arc therapy were based on the cyclotron or synchrocyclotron accelerator system such as IBA's Proteus product. At the time of writing of this article, PAT development and

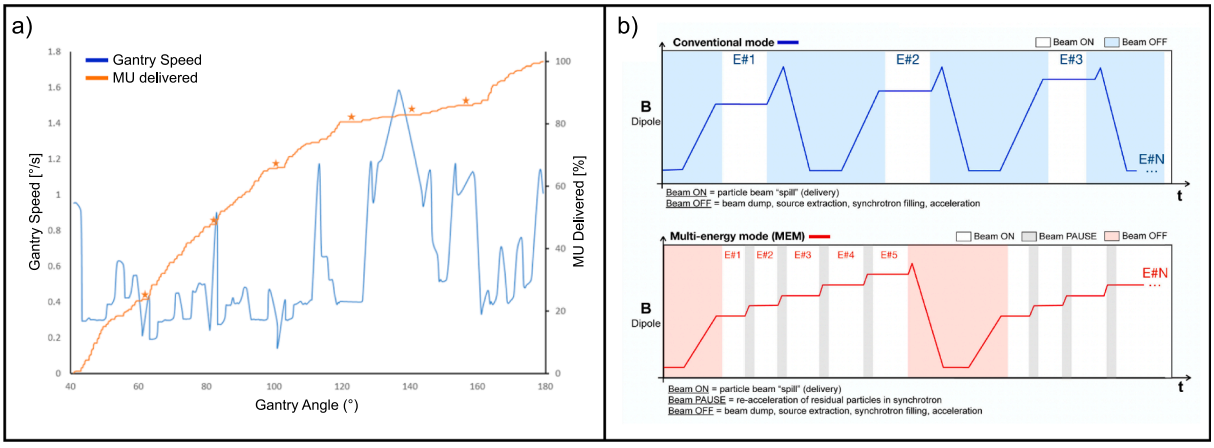

Fig. 4. Delivery characteristics for different accelerator types for developing robust and efficient arc delivery: (a) gantry speed and MUs delivered versus gantry angle for a cyclotron-based prototype proton arc therapy system. (b) SEE versus MEE mode for synchrotron-based facilities.

investigations using synchrotron-based PBS systems are limited. Conventionally, synchrotrons use the single energy extraction (SEE) process, which involves acceleration and extraction of ion bunches of a single energy for irradiation per "spill" or "cycle" [91]. Once all spots for a particular energy layer are delivered, the remaining particles within the synchrotron ring undergo deceleration and are subsequently discarded. Therefore, SEE requires a spill change for each energy layer. The conventional SEE extraction method, characterized by a typical cycle/spill change time (including beam dump, source injection, and acceleration) of several seconds and spill lengths ranging from a few to tens of seconds, may not be well-suited for efficient arc therapy delivery. As discussed in section 1 on treatment planning and optimization, the application of SEE may be highly inefficient for synchrotron-based SEE systems since many energy changes may be required for robustness to ensure target coverage, improved conformity and reducing the impact of uncertainties. However, multi-energy extraction (MEE) techniques have been developed [92–94] and implemented for clinical use in particle therapy. MEE facilitates efficient in-spill energy changes by successively accelerating or decelerating the remaining particles in the synchrotron to the next planned energy layer, reducing the frequency of beam dumps. Previous study has shown that MEE improves beam delivery efficiency and effectively reduced BDT, with in-spill energy switching times of < 200 ms [93]. Still, it is important to note that MEE is limited by several factors, including the maximum charge available in the synchrotron for extraction, the method of energy change and the consequent loss of extractable charge during energy switching, the maximum extraction time during which a stable beam can be extracted, and limitations in the control system such as the number of MEE layers (i.e., memory and calibrations). Nevertheless, technological advancements have led to substantial improvements in machine operating parameters. A study on the Hitachi synchrotron has shown a significant reduction in BDT with the most up-to-date system compared to a system installed 10 years ago, with both systems configured with MEE [95]. Furthermore, continuous scanning provides the potential for further reduction of BDT [83].

For carbon ion therapy, currently all clinical facilities are synchrotron-based, some of which still operate using SEE techniques. However, MEE techniques for carbon ion therapy have also been developed and implemented for clinical use (Fig. 4.b) [92–94,96,97]. Multi-energy synchrotron operation with an ELST of ~ 200 ms has been achieved [97]. Together with fast ion species switching techniques, MEE techniques have been applied to multi-ion irradiations using helium, carbon, oxygen, and neon ions at the National Institutes for Quantum Science and Technology (QST) [96]. Nonetheless, MEE is still not widely adopted and should be further developed and tested for clinical application. In the context of arc delivery, MEE with such fast energy switching has a potential to enable more energy layers within a typical treatment delivery time which could further support feasibility and efficiency of robust PAT. Simulation studies propose and investigate PAT delivery using SEE and MEE techniques for carbon ions [53,59] but beam delivery characteristics using SEE and MEE techniques should be further investigated in the context of PAT, such as the beam optics settings and stability, i.e., energy, focus, and intensity. Dedicated efforts to optimize beam delivery parameters and sequences have yet to be investigated for both $PAT_{step\text{-}and\text{-}shoot}$ and $PAT_{dynamic}$ using ions heavier than protons. In terms of novel accelerator design for carbon and helium ions, development of the IBA C400 is underway [98,99], which could mark the first compact superconducting isochronous cyclotron capable of delivering proton, helium and carbon ions. This system could be particularly useful for heavier ion beams, given delivery characteristics and efficiency are similar to that of proton therapy cyclotrons.

In sum, optimizing the number of energy layers and minimizing the time required to switch energy layers is essential for creating robust arc treatment plans and enhancing delivery efficiency. Cyclotrons and synchrocyclotrons for PAT are advantageous due to their ability to provide a continuous beam supply, which simplifies beam delivery and infrastructure, potentially reducing delivery time and leading to a more compact design. In general, cyclotron-based systems typically achieve higher beam currents compared to synchrotrons; however, their fixed energy output, requiring external energy degraders for energy variation, can limit treatment flexibility and precision particularly at facilities with larger range shifters requirements (~7 cm). Synchrotrons with a fixed beam accelerator radius offer precise control over beam energy and allow for multi-particle facilities (currently, there are no multi-ion cyclotrons in clinical use), enabling a wider range of PAT treatment options. However, synchrotrons come with more complex and larger infrastructure — various sources of variability, such as the beam extraction/BDT and pulsed nature of the beam, need to be managed to maintain precision. Rapid energy switching capabilities like MEE are promising especially for ion therapy facilities. Despite these capabilities, synchrotrons generally produce lower beam currents than cyclotrons, which may affect treatment time efficiency especially for large scanning volumes. For PAT, system attributes and constraints specific to each accelerator type have yet to be fully studied and realized beyond BDT models. Nonetheless, addressing challenges in optimizing accelerator characteristics and the BDT models for PAT is necessary and will involve the development of different strategies (for the latter, see section 1 on planning). Each approach will have its pros and cons, but ultimately the optimization strategies should be based on the available technology and characteristics of the machine-specific beam delivery sequences.

Gantry-based systems

Similar to how current VMAT systems use the rotating LINAC gantry, one type of PAT delivery involves using gantry rotation. Given that these gantry systems are massive scientific instruments weighing approximately 100 tons or more, dynamically delivering the ion beam while rotating requires significant dedicated development to ensure precision, efficiency and safety. Since 2018, proton arc therapy solutions have been under development by IBA (DynamicARC®). As opposed to IMPT, control points define the gantry angles, tolerance window, energy layers and spots so that the gantry can rotate while delivering the proton irradiation following the sequence of the control points (Fig. 5) [28]. Technical developments include new electronic units for both gantry control and delivery control. As opposed to conventional PT systems, these two control units should now communicate during treatment delivery and synchronize their actions, which is necessary for an accurate and efficient PAT delivery system. More specifically, the gantry speed can be adjusted dynamically according to the gantry position feedback and treatment delivery progress. Several safety systems are used to ensure safe treatment delivery, such as redundancy in the control units, hardware console, and proximity management. One advantage of approaches like DynamicARC® is that they can be retrofitted on existing Proteus®ONE and ProteusPLUS® systems [11], as opposed to complete system redesign. In general, development of $PAT_{dynamic}$ may be more streamlined when using lighter compact gantry systems intended for arc delivery.

Currently, there are 14 ion therapy facilities operating clinical programs with helium and/or carbon ion beams, and most host fixed-beam lines only. Gantry systems for heavier ions are still rare and costly (due to the immense size of ~ 200–700 t). At the moment, there are only four facilities with operational heavy ion gantry systems located in Germany, Japan, and South Korea. Nonetheless, the increased degrees of freedom in beam angle selection using a gantry system provide advantages for specific disease sites and indications [100,101].

The techniques in particle therapy involving gantry systems evolved naturally, like in conventional radiotherapy, toward rotational intensity modulated therapy. Proton arc delivery using a gantry system is already a highly complex undertaking and given access to a gantry system for carbon ions, delivery methods could theoretically be performed using step-and-shoot or dynamic using co-planar or non-coplanar arcs [11]. Dynamic delivery could be readily achievable for ions arcs, especially considering novel accelerator technologies in development, e.g.

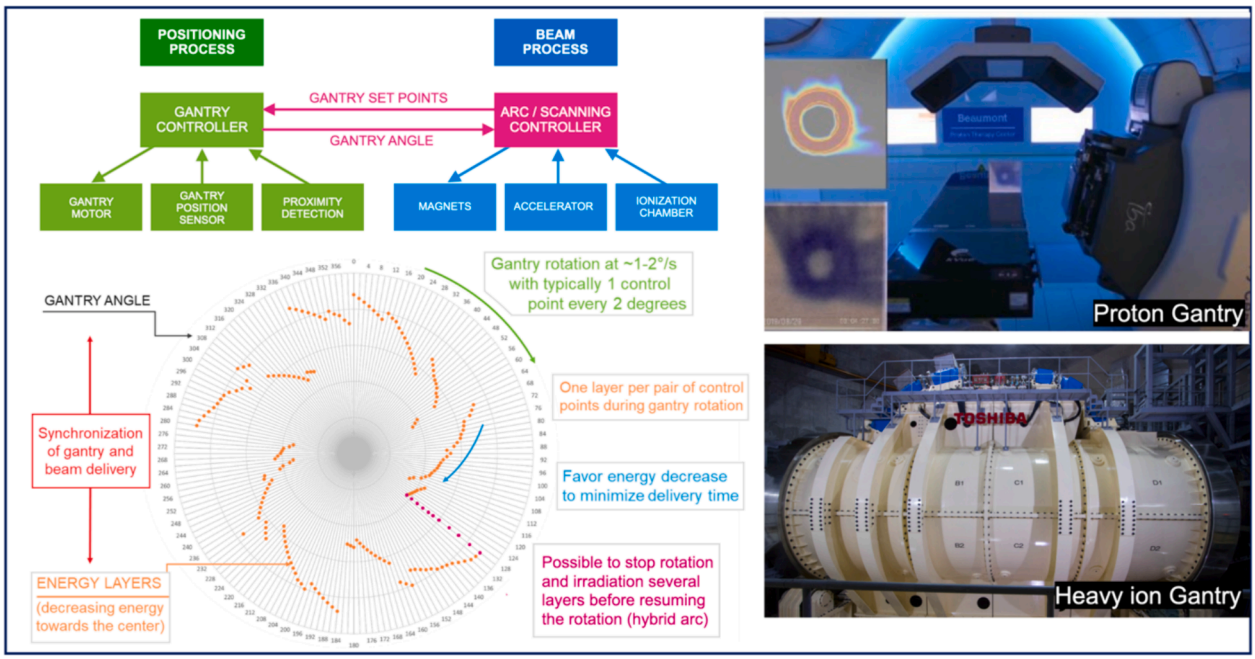

Fig. 5. Gantry-based PAT system workflow [109], featuring images of proton and heavy ion gantry systems. The prototype proton arc system demonstrated the first dynamic delivery using film measurements. PAT delivery has yet to be demonstrated using a heavy ion gantry system (e.g., the super-conducting gantry system at QST [110,111]).

quantum scalpel [102–104] multi-ion cyclotrons [105], compact gantry systems and/or upright PPS. However, given the current state of gantry technology and hardware at facilities like the Heidelberg Ion-beam Therapy Center (HIT) and QST, which host several ion sources [106], $PAT_{step\text{-}and\text{-}shoot}$ could be the first version and most feasible arc therapy mode. One disadvantage to gantry-based systems for $PAT_{dynamic}$ is that beam optics can significantly vary with gantry angle. To account for this, specific gantry angles are commissioned, and unique beam-line settings are used for each angle and energy to ensure the correct beam parameters by the quadruple focusing magnets (e.g., small corrections to the beam size/position as a function of the gantry angle) [107]. $PAT_{dynamic}$ with such systems may pose challenges or non-ideal beam optics as opposed to fixed-beam (gantry-less) delivery, as discussed in the following section. Fortunately, the heavy ion gantry has been significantly downsized using an XY combined type scanner and a super-conducting magnet with a maximum dipole field of 3.5 T [108]. Vendors like Toshiba and Hitachi also propose lighter super-conducting gantry systems. The heavy ion gantry systems installed in Yanagata and Yonsei University have an axial length of ~ 8 m and a rotational radius of ~ 6 m, which is about 1/3 of the heavy ion gantry at HIT. For super-conducting gantry systems, efficient implementation of ion arcs may pose additional challenges due to hysteresis of the beamline magnets, which has yet to be investigated in the context of PAT. Nonetheless, both proton and heavy ion gantry systems that exist today were not originally designed with the intention of arc delivery and consequently, hardware and software upgrades for accelerator, beam delivery, and gantry control systems may be required to perform efficient arc delivery. Most carbon ion facilities host a fixed beamline; therefore, a gantry-less approach to arc delivery, like upright positions and treatment chairs, could be particularly attractive and cost-effective for rotational delivery techniques.

Gantry-less delivery

In the early days of radiation therapy, most treatments were done in the upright orientation. The late diagnoses of cancers (in the early days) led to patients being very sick and less ambulatory, requiring imaging and treatment technologies to be done in a non-recumbent position. Today patients are generally more ambulatory allowing for radiological procedures in the generally more comfortable upright orientation. Developing upright diagnostic imaging and treatment technologies are now gaining interest and are complementary with PAT developments. A recent review assesses current designs for particle therapy systems, particularly chair setups and their accompanying image guidance, culminating in recommendations for incorporating findings from the literature into future upright treatment configurations for both existing and new facilities [78]. Leo Cancer Care, for instance, developed an upright PPS that can position the patient comfortably in a seated or perched (semi-standing) position with an on-board dual-energy CT system (Fig. 6). Upright positioning offers reproducible patient posture and comfort, supported by 6-DOF bases for precise treatment positioning; a large precision bearing facilitates patient rotation, and continuous rotation is enabled via a slipring, making it ideal for arc treatments using fixed beamlines. Recent research by Bosbouvier *et al.* highlights improved patient comfort in upright positioning, suggesting its potential to enhance particle therapy with arc beam delivery, especially for facilities lacking gantry systems [112]. Gantry-less treatment rooms with a fixed-beam nozzle and patient-based rotation devices as described could be more cost-efficient compared to gantry-based systems and further streamline arc delivery, especially in carbon, oxygen and neon ion therapy. PPS and dedicated accessory imaging, such as vertical CT, PET and MRI, still need to be developed and translated into the clinic which may increase the initial investment cost and future clinical operation complexities [113].

Before upright PPS can be utilized in clinical routine, however, several challenges need to be solved. Currently, the largest uncertainty relates to anatomical differences between upright and recumbent patient positioning. Differences between supine and upright posture were observed for the thorax regarding lung volume, breathing motion [114–118], heart shape/position, abdominal organs, such as kidney, spleen and liver [119–121] and even for the pelvis region, e.g. bladder and prostate position. In addition, patient posture (e.g., arms up or down) needs to be carefully evaluated for upright PAT. For upright PAT, the incline angle of the backrest of the patient immobilization device typically used for comfort and stability [78] also defines the delivery

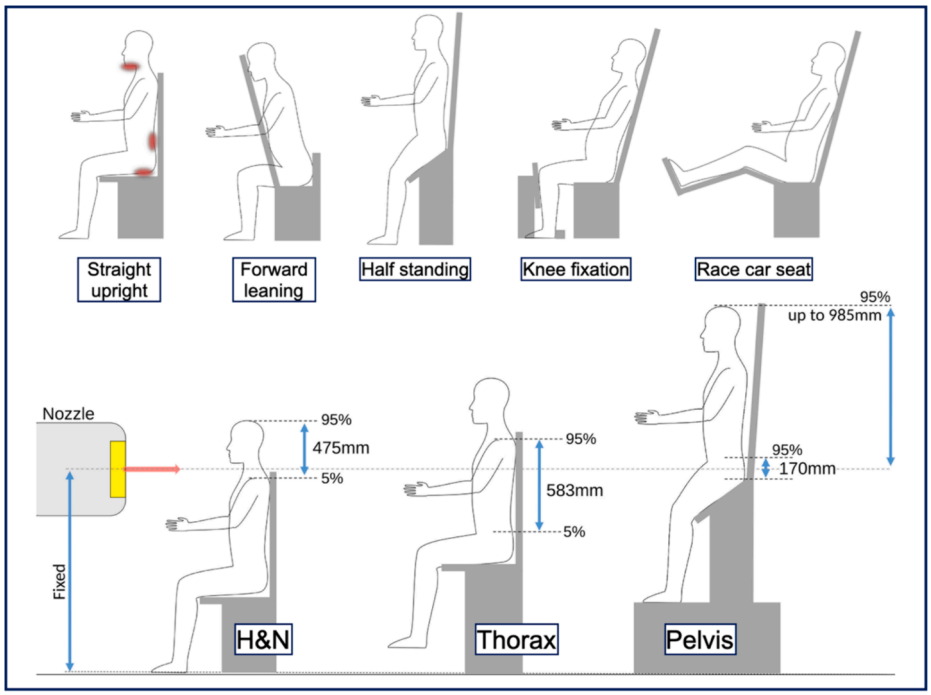

Fig. 6. Gantry-less delivery systems, i.e. upright PPS, under development in the industry compatible with arc delivery [11,59]. Various patient positions for different treatment sites can be used. A schematic overview of different postures and required vertical ranges (not to scale) of adjustment for different treatment sites are provided [78].

plane for coplanar arc, which may not be aligned to the vertical planning CT scan cardinal axes. Non-coplanar PAT in upright position would require a change in patient posture during rotation which likely introduces further anatomical and setup differences.

Further, there are open questions regarding patient setup and QA, in particular on the use of immobilization equipment such as thermoplastic masks and vacuum cushions with upright patient postures [78]. Patient specific QA for upright PAT will not only require suitable detector equipment capable of 3D dosimetry on the rotating patient positioning system but will also include verifying the stability of the positioning and immobilization system and its rotational synchronization to the beam delivery system while under load (for realistic deformation and acceleration/deceleration). Log-file based dose reconstruction that takes the PPS rotation as additional input combined with time resolved 2D measurements might be suitable also for patient specific QA of upright PAT (see section 2.2.5 on dosimetry and QA). To synchronize the delivery with the rotation, a direct connection between the upright positioning system and dose delivery system needs to be established, including relevant interlocks. Matching patient rotation and plan progress requires adjusting the particle rate to the rotation or vice versa, and/or beam gating. For patient rotation, the most important parameter is the patients' tolerance limit for the angular velocity and acceleration. Whelan *et al.* found no significant issues for patients at rotation speeds of 2 rpm regarding motion sickness and anxiety [122]. As particle therapy gantries typically rotate at speeds of ~ 1 rpm, the same or even faster PAT delivery may be achievable with rotating patient systems compared to gantry-based delivery.

Aside from arc delivery technology using fixed-beam nozzles, several works outside the commercial sector propose development of next-generation delivery which could be directly compatible with arc delivery. For example, a static magnetic system utilizing concentric coils for proton arc therapy has been designed at the Paul Scherrer Institute and patented (US-20210001150-A1), which eliminates the need for both gantry and patient rotational systems [123] (see Supplementary Document). This novel approach allows for precise beam guidance along a circular path around the patient within a static magnetic field and precise bending using an enclosed, stronger inner bending field. Adjustment of the treatment angle is achieved by varying the strengths of arc-scanning magnets, enabling rapid delivery of large arcs and facilitating non-standard dose delivery sequences, potentially revolutionizing particle therapy accessibility. Other works present novel concepts for a "non-rotating' toroidal gantry for hadron therapy [124]. Ultimately, these gantry-less technologies could enable rotational particle therapies while reducing facility costs associated with gantry systems.

PAT delivery in step-and-shoot mode ($PAT_{step\text{-}and\text{-}shoot}$)

In general, particle arc therapy can be considered an advanced IMPT planning, with the treatment modality consisting of numerous gantry angles. Therefore, before $PAT_{dynamic}$ is clinically implemented, $PAT_{step\text{-}and\text{-}shoot}$ can provide an alternative solution for deliverability using the state of technology at existing particle therapy facilities with a similar degree of freedom, though treatment delivery may not be as efficient as the $PAT_{dynamic}$ approach. Works suggest that $PAT_{dynamic}$ may be faster than $PAT_{step\text{-}and\text{-}shoot}$ as it fully uses the delivery window without the need to stop the gantry or PPS [125]. That said, $PAT_{step\text{-}and\text{-}shoot}$ mode is less demanding technologically as it does not require a dynamic rotational gantry or PPS [71]. Therefore, to ensure efficient delivery, auto-sequencing should be implemented for $PAT_{step\text{-}and\text{-}shoot}$, i.e., as opposed to current conventional delivery, which involves manually loading field-by-field, pausing for preparation of the subsequent beam, gantry rotation, couch motion, snout repositioning, and beam/spill request. It was reported that treatment plans with dozens of fields offer similar distributions and treatment features as $PAT_{dynamic}$ and better plan quality than IMPT with limited beam angles [57,126]. Some existing energy layer reduction and selection methods could be used to generate an efficient plan [71,73,74]. Additionally, to implement $PAT_{step\text{-}and\text{-}shoot}$ practically and efficiently, Engwall *et al.* proposed an approach for partitioning into subplans to be delivered interlaced over different fractions in the treatment course [57]. Lastly, combining both step-and-shoot and dynamic delivery mechanisms, hybrid arcs may be needed in some specific cases in the particle TDS, where some beam

directions/control points require much more irradiation time than others.

Dosimetry and quality assurance

As particle beam therapy becomes more popular and accessible for treating cancer, the consistent and high-quality clinical commissioning standards and procedures, and comprehensive quality assurance (QA) guidelines and methodologies to determine these guidelines for proton therapy delivery—will be essential to ensure that patients are treated safely, precisely and effectively. AAPM Task Groups 185 and 224 were therefore charged with describing the considerations needed to define how to perform the commissioning of the intensity-modulated scanning proton therapy systems and ancillary systems, and the QA procedures (beam delivery mechanisms, beam parameters, and instrumentation) and identifying examples of comprehensive QA procedures for proton therapy machines [127,128].

As the advancement of PAT would afford dynamic irradiation during gantry rotation to achieve fast treatment delivery and very conformal dose distribution, new challenges arise during the acceptance test, clinical commissioning, and QA processes, and compared to traditional IMPT. Similar to VMAT QA systems, which verify synchronization of gantry rotation and beam delivery parameters, e.g., dose rate and the MLC positions, QA systems for PAT must be designed be reliable in catching planning and machine errors in a rotational system. Several additional procedures and tests dedicated to arc delivery may need to be performed, which include but are not limited to following:

- Beam parameters such as spot optics, beam energy/range and other delivery sequence/parameters would have to be specified by the vendor, measured, and checked at gantry dynamic mode during the acceptance test phase.
- Regarding the commissioning, the accuracy of machine log files and gantry rotational accuracy may need to be checked carefully with an independent inclinometer.
- For machine and patient-specific QA, the dose measurement and verification must be done interactively with dynamic arc irradiation and gantry rotation.
- The workload for medical physicists and the efficiency of performing the above should be clinically acceptable.

Preliminary consensus and perspective on the ESTRO physics workshop indicate that dosimetry detectors currently used in IMPT would still be relevant for acceptance tests, clinical commissioning, and in-plane QA of the particle arc delivery technique. However, rotation synchronization between dosimetry equipment, gantry and/or PPS is the key to ensuring accurate measurements during the $PAT_{dynamic}$. Therefore, gantry-mounted nozzle holders and isocentric 360° rotating couch holders are being developed for the existing 2D measurement devices. Both gantry-mounted and stationary QA solutions may be particularly valuable for detecting potential deviations in spot/raster-scanning patterns while dynamically rotating the beam or patient, i.e., differences in planned versus delivered 3D spot maps resulting from errors in the synchronization of scanning sequence and arc trajectory. Dedicated QA tools and procedures should verify the stability of the mechanical and radiation isocenter, if applicable, during the dynamic rotation of the gantry system or Patient Positioning System (PPS). These QA measures are critical to ensure that for all gantry angles in the arc delivery, angular-dependent corrections are accurately applied to steering magnets to compensate for deviations in mechanical and radiation isocenter due to gantry sag. Fig. 7 demonstrates the first machine QA (mechanical/radiation isocenter stability) and patient-specific QA tests for a proton arc system, where a dedicated nozzle mount was fabricated to hold an ionization chamber array at a fixed distance from the source position during dynamic rotation and beam delivery.

As for 3D or quasi-3D dose verification, dedicated cylindrical phantoms could be an option worth exploring, e.g., a device analogous to the ArcCHECK® (SunNuclear Corp), OCTAVIUS/ RUBY® (PTW or Delta4 (Scandidos) for IMRT/VMAT delivery verification or gel dosimetry [129]. In conjunction, treatment machine log files (which include the nozzle ionization chamber readings of spot position and monitor units as well as gantry angles and time structure) could be used to reconstruct the dose in the 3D patient anatomy using an independent Monte Carlo dose engine. However, one must note that despite the potential for efficient virtual QA, log-file usage in particle therapy is still scarce. Clinical application in QA is not widely adopted and most works published present as proof-of-concept [130–134]. Further analysis with dose evaluation tools (gamma index, DVH, clinical goals, etc.) could then be performed to compare the reconstructed dose with the TPS results, as well as having tools for automatic evaluation of data as a function of time or beam angle. This alternative solution should be realized through commercial QA software, such as myQA iON (IBA Dosimetry), Mobius3D (Varian) and ClearCalc (RADformation), which allows for software-driven efficient, accurate, and safe methods for periodic and patient-specific QA.

3. Clinical outlook

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Planning studies

Pencil beam scanning has become the standard of care for proton therapy world-wide due to its inherent automation and flexibility, as well as its potential to substantially reduce integral dose to normal tissues. IMPT is a highly degenerate treatment technique, i.e., many different dose delivery patterns, field arrangements, spot positions and weights of Bragg peaks can result in similar target coverage and dose homogeneity [24,135]. Nevertheless, there are limitations to current implementations of PBS proton therapy, particularly the delivery efficiency and, for some indications, an inferior lateral dose penumbra in comparison to state-of-the-art photon delivery technologies [136–139]. Following on from the undoubted success of the introduction of arc therapy techniques into conventional photon therapy, and as a consequence of the (almost) fully automated delivery of PBS proton therapy, arc approaches to PBS proton therapy are now being developed for eventual clinical translation.

Since PAT has not yet been used to treat patients, planning studies are currently the primary source of information about its potential clinical benefits. To-date, numerous *in silico* studies have investigated the advantages and drawbacks of proton arc therapy across diverse treatment sites, aiming to gauge its clinical value over IMPT. These investigations assess the ability of either $PAT_{dynamic}$ and $PAT_{step\text{-}and\text{-}shoot}$ to maintain optimal target coverage, conformity, and dose uniformity while improving robustness and sparing organs at risk (OARs) to reduce normal tissue complications.

Initial studies tested basic arc plans for thoracic [140,141], and abdominal cases, showcasing improved target coverage and conformity. Later developments introduced more sophisticated multi-beam techniques and full dynamic arcs, with studies comparing IMPT and arc plans for various cancers, like brain [142], H&N [71,143,144], prostate [145], breast [55], hepatic [146] and in pediatrics [147,148]. These studies evaluated target coverage, plan quality, OAR sparing, robustness, interplay effects, and delivery time. Overall, these studies on proton arc show that target coverage and plan homogeneity are maintained compared to IMPT while enhancing conformity and substantially sparing OARs. Notably, PAT plans have the potential to reduce treatment time and patient body integral dose across a wide range of patient geometries and clinical indications. Compared to IMPT, PAT irradiates the beam through arc trajectories which increase the low dose bath

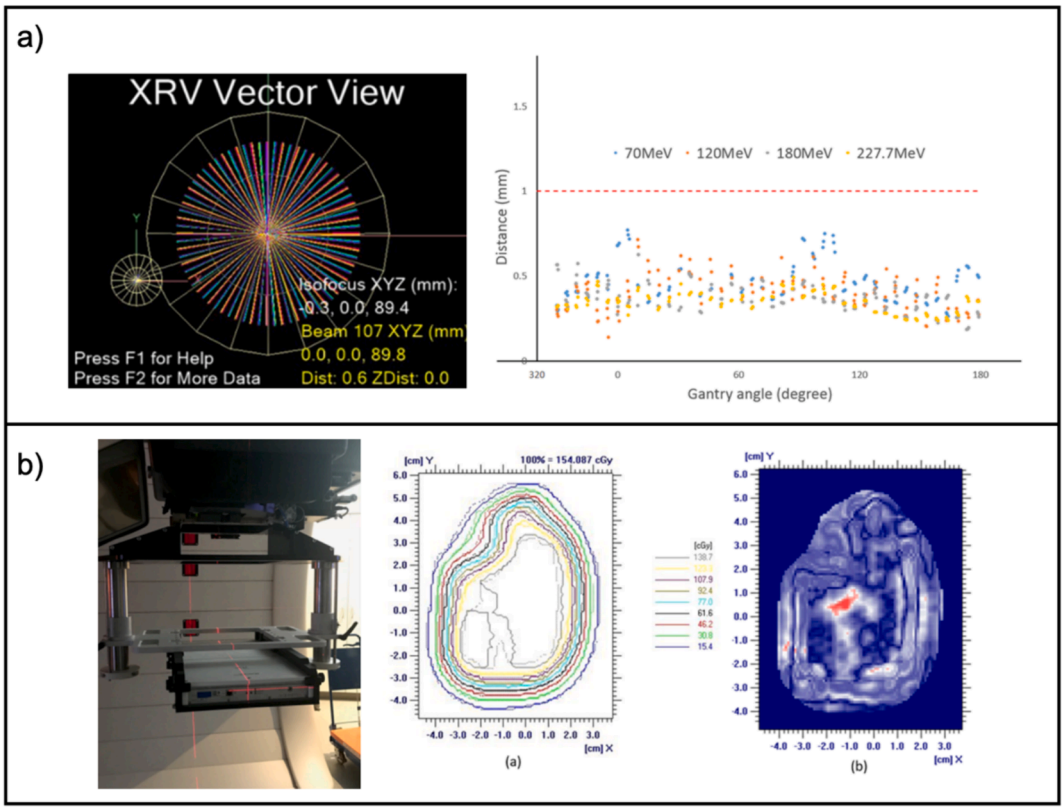

Fig. 7. (a) Proton arc therapy *iso*-centricity check (dynamic gantry angle rotation vs radiation *iso*-center) using XRV-100 (logos system International, Scotts Valley, CA, U.S.A.), a cone-shaped scintillator detector. The result showed that the *iso*-center agreements are within 1mm radius from 70 to 227.7MeV based on the prototype IBA ProteusONE DynamicARC® system. (b) Patient-specific plan QA (PSQA) measurement using a gantry-mounted 2D ionization chamber array (IBA dosimetry, Louvain-la-Neuve, Belgium) which showed a good agreement between the nominal plan (middle) and the measurement (right).

volume. On the other hand, dosimetrists may choose beam angles for IMPT which may be ideal given site or case-specific considerations but may not necessarily represent the shortest beam path to the target compared to PAT inverse optimization [149]. Furthermore, PAT plan robustness against uncertainties and interplay effects needs further study. Other studies comparing proton arc therapy to interstitial high-dose-rate brachytherapy for gynecologic cancer patients with parametrial/pelvic side wall extension revealed that proton arc therapy could offer a noninvasive alternative with superior dosimetric outcomes [150,151]. Using advanced optimization algorithms like SPArc, or commercial proton arc products in RayStation and Monaco may further improve plan quality, OAR sparing, and toxicity reduction. For PAT using heavier ions, sites that often involve the treatment of radio-resistant disease should be a primary focus, especially where high linear energy transfer (LET) boosting could be beneficial.

Despite these promising initial results, further evaluation across diverse treatment sites and patient selection strategies is necessary, especially after the first clinical planning and delivery systems are commissioned for arc delivery. Studies should investigate plan robustness in-depth against both physical and biological uncertainties and interplay effects on dynamic rotation/delivery. Most of the existing site-specific reports were conducted by the same few groups, some of which apply in-house developed planning systems [152–155]. It's therefore imperative that clinical treatment planning and delivery tools be made available for other clinical and research groups to conduct independent studies. In the following section, key clinical perspectives are explored, including radiobiological considerations, potential clinical studies and applications, and synergies with other promising delivery techniques.

Radiobiology

Integral dose and integral effect

The main dosimetric advantage of proton therapy over photon therapy is often simply summarized as a reduction in the integral dose, which if the dose is integrated over the mass of the patient equals the total energy deposited in a patient. For the same high dose region, the integral dose is always lower with proton treatments, regardless of which photon treatment modality is used. This assessment of proton therapy may be too simplistic because the integral dose does not provide any information about how the dose is distributed [138]. In addition, the amount of integral dose reduction with protons depends on the location of the tumor. For example, for some superficial tumors, protons allow dose conformity without a low-dose bath, whereas for more centrally located tumors, there will obviously be dose in the entrance region. In the context of proton arc, the question is whether a low dose to a large volume (proton arc) is advantageous compared to a high dose to a small volume (as in IMPT). To properly assess the benefits of proton arc therapy, the potential effects of either increasing or decreasing integral in certain tissues must be compared against IMPT and photon-based therapies. Furthermore, planning studies provide data on the integral dose between IMPT and PAT for different clinical indications and treatment scenarios. For instance, Toussant *et al.* studied the risk of second primary cancer in pediatric brain tumors and found that using PAT, integral dose was reduced by a median of 29% compared to VMAT, and 17% compared to IMPT [148]. However, results are expected to vary with optimization technique and parameters (e.g. arc trajectory, energy sequence, etc.), as well as treatment depth and target volume. The evaluation of radiation induced secondary malignancies is multi-factorial including aspects that must be taken into account with caution such as age, gender, genetics, fractionation, organ, concomitant

treatments and others, with a special consideration for pediatric patients [156].

The dose distribution must also be considered when assessing the potential treatment outcome. The biological consequence of differences in dose distribution depends on the sigmoid dose–response curve for normal tissue complication probability (NTCP). Obviously, if the NTCP is already low, i.e., in the flat part of the dose–response curve, the effect of dose levels is much less than in the steep part of the dose–response curve. Particular consideration should be addressed related to reirradiations, a clear indication of proton therapy [157].

Another aspect of integral dose that has received much attention recently is related to radiation-induced lymphopenia. It is well known that radiation-induced lymphopenia correlates with treatment outcome, and there is concern that irradiating large volumes of blood may have a detrimental effect on the lymphocyte population and thus reduce the patient's immune response [158]. In this regard, not only the dose distribution but also the duration of dose delivery plays a role [159]. With a more homogeneous low/mid-level dose distribution and a longer delivery time, a greater effect on lymphocytes could be expected with proton arc compared to IMPT. Further research is needed to understand proton arc treatment delivery time compared to IMPT and the impact on lymphocyte population and the immune system at large.

Another relevant radio-biological study for particle arc delivery is the phenomenon of low dose hypersensitivity, which refers to the unexpectedly high radiosensitivity of cells at doses below ~ 0.5 Gy [160]. With single doses of low LET ionizing radiation, the amount of damage is thought to be too low to trigger the full extent of cellular DNA damage response, which models suggest involves damage recognition, signal transduction, and damage repair [161]. Consequently, when larger volumes of these low doses are used in PAT with conventional fractionation schemes, there may be a significant difference in the biological effects on normal tissues that are not currently considered in clinical practice. This raises the possibility of exploring the value of hypofractionation schemes for particle arc treatments, evaluating in parallel the incidence of hypofractionation on the previous discussed effects (secondary malignancies and lymphopenia).

LET and RBE

In assessing differences in proton therapy dose distributions between IMPT and PAT, we need to look beyond dosimetric indices, despite the generic relative biological effectiveness (RBE) of 1.1 used in clinical current practice [162]. Although it is unclear whether clonogenic cell survival data are relevant for assessing in vivo toxicities, data suggest that the RBE increases with decreasing dose [163]. This could have a negative impact on the RBE-weighted integral dose when the dose is distributed over a larger volume, as in proton arc therapy. Nonetheless, the entrance channel doses are mostly attributable to lower LET particles and, therefore, exhibit lower RBE compared to the same dose level for higher LET in the SOBP and at the distal edge.

The RBE also depends on the LET, with an increase in RBE as the LET increases, typically observed at the end of the range of individual proton beamlets [164]. The distribution of LET can be very complex in an IMPT-based dose distribution, but due to the inherent degeneracy of IMPT plans (i.e., the potential to deliver apparently identical plans with different fluence maps), LET distributions can be controlled to some extent, which is exploited in LET-based optimization [165]. Typically, LET hot spots can be moved away from critical structures, but it is rarely possible to move these regions of elevated LET completely into the target. This ability improves with an increasing number of fields, allowing LET hot spots to be placed in the target volume with techniques such as proton arc. LET-optimization methods first focused on reducing the LET in critical structures, not so much on increasing the RBE-weighted dose in the target as seen in PMAT. Dose escalation or removing target dose homogeneity constraints to allow for hot spots can alternatively be performed as in SRS/SBRT; however, for certain indications (site and target size), such approaches may not be feasible due to OAR constraints and physician preference [166].

LET_d levels in the target volume can be optimized to be higher for proton arc versus conventional PBS delivery with limited beam angles, and this level of LET_d enhancement has been studied in vitro, showing an RBE enhancement compared to the clinically applied assumption of 1.1 [167]. For instance, a study predicted RBE enhancement with variable RBE models and measured an increased RBE in vitro for proton arc against IMPT (mean target LET_d values of ~ 3.2 keV/um and ~ 4.2 keV/um for IMPT and proton arc, respectively). However, the implementation of this RBE variation in the TPS is still a subject of debate, as discussed in the AAPM Task Group Report 256 [168]. One could argue that having a larger volume of higher-LET in the tumor and a reduction of higher-LET exposure in organ at risk (OAR) structures may indirectly benefit patients, as the differences between conventional and arc delivery might be negligible during planning. This suggests that the current proton therapy planning procedure can be maintained for proton arc, i.e., constant RBE. Regardless, it must be emphasized that by focusing LET on the target, one can increase the effectiveness of the radiation to the extent that the planned physical dose required to induce the same effect could be reduced. As such, PAT could not only reduce the LET in the normal tissue, but also reduce the dose to the normal tissue, while maintaining or even increasing the TCP. In other words, PAT can effectively reduce the total physical dose delivered by increasing LET (and, in turn, RBE dose) in the target. Recent publications reported that PAT techniques which boost target LET_d could be more biologically effective than IMPT via experimental validations in vitro [167]. Admittedly, this "exchange" of dose and LET is an unexplored venue of dose optimization and calls for further development and study. Further studies are needed on biological read-outs for arc, RBE modeling and performance in arc therapy dose/LET distributions. For proton arc, it has yet to be determined whether clinical benefits due to modest increases in LET_d in the target volume using full or partial arc treatments (a few keV/μm) outweigh the inevitable increase in low-dose bath compared to IMPT. With respect to PAT using heavier ions, however, LET_d boosting strategies are promising in addressing radio-resistant disease and deserve dedicated radio-biological investigations.

When considering higher LET particles like carbon ions, higher efficacy may be achievable since the uncertainty of response for carbon ions is reduced due to dependency on physical and biological factors, such as genetic background, tumor microenvironment, heterogeneities, and other patient-specific factors, e.g., HPV status, oxygen status, and tumor heterogeneity, etc. [60,169,170]. Enhancing high LET distributions is theoretically possible with IMPT beams but at the cost of reduced robustness and increased dose in entrance channels that might be unsuitable for OAR, leading to potential toxicity [12]. Thus, maximizing the high LET components in the target via arc delivery (Fig. 3) could provide a more biologically robust and high-precision treatment option for specific indications, addressing both intra- and inter-patient variability in treatment response. Further site-specific studies are needed to identity indications and sites which would benefit most. Fig. 8 presents a comparison of SHArc with carbon ion beams against IMPT (with and without LET optimization) using two posterior oblique fields as performed in clinical practice, demonstrating increased LET_d in the GTV, and reduced higher LET components in the normal tissues. Generating similar levels of LET_d enhancement using IMPT may be feasible by adding several more beam angles (e.g., anterior and lateral obliques); however, delivery efficiency and dosimetric features may be less optimal and IMPT versus $PAT_{dynamic}$ for carbon ions has yet to be investigated. Nonetheless, these results suggest SHArc may be particularly useful for overcoming radio-resistances, for example, recent analysis of carbon ion treatments for pancreatic cancer showed a correlation between that minimum LET in the GTV and local control [171]. As discussed in sections 1 and 2 on treatment planning, optimization and delivery, multi-ion therapy (MIT) is an emerging particle therapy delivery technique, whereby mixing lower LET (proton and helium) and higher LET (carbon, oxygen and neon) particle species affords increased degrees of freedom

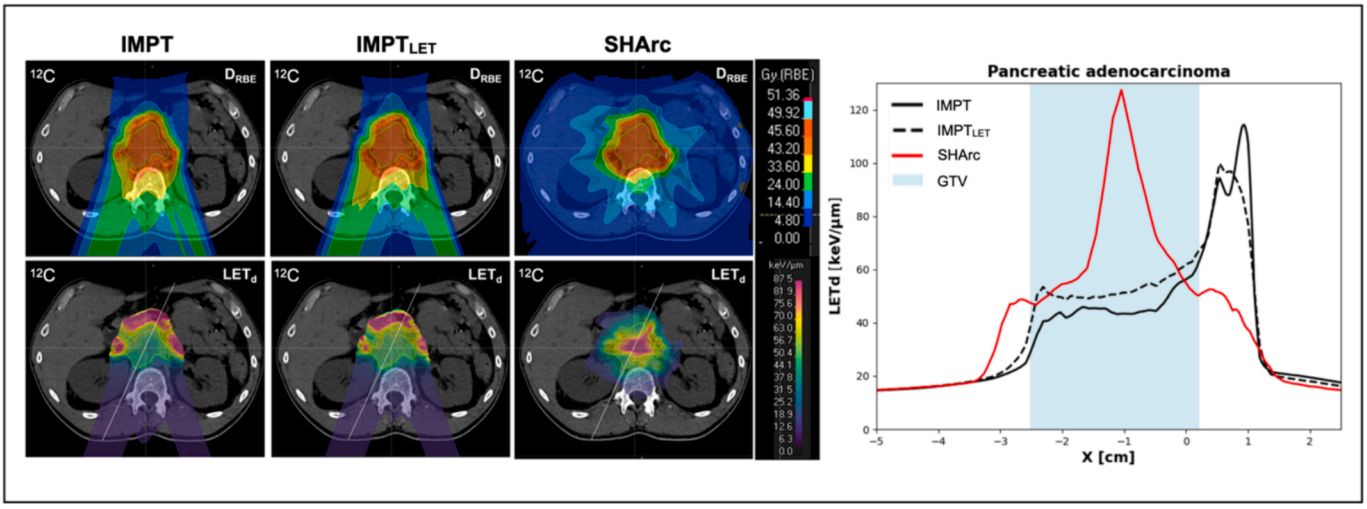

Fig. 8. Biological dose (D_{RBE}) and LET_d maps for a pancreatic adenocarcinoma patient case using carbon ions. Three different treatment planning cases are presented: the clinically applied IMPT plan (IMPT), IMPT applying LET_d optimization to enhance LET_d in the GTV ($IMPT_{LET}$) and PAT (SHArc). LET_d values are displayed with a 20 Gy low-dose threshold. The white lines in the LET_d map designate the LET_d profiles presented, highlighting the LET_d range within the GTV [177].

in treatment design, e.g., generate uniform RBE/LET distributions or boost LET_d in specific target structures [68,172–174]. SHArc can similarly provide LET_d enhancement using carbon ions for facilities that do not host multiple novel ions, e.g., helium, oxygen, and neon ions. However, the two concepts are not mutually exclusive and recent works present treatment optimization for combining MIT and PAT, which afforded both LET_d enhancement and a more homogenous physical dose in the target volume [59]. Future works should investigate the clinical merit of SHArc to increase "biological robustness" using high LET_d enhancement in the tumor for specific treatment sites.

Furthermore, heavier ions, such as helium, carbon, oxygen and neon ions, exhibit a sharper Bragg peak and lateral/distal penumbra compared to protons [175], potentially affording increased tumor conformity than protons [12]. However, compared to protons, heavier ions undergo a more complex cascade of nuclear reactions which generate high energy particles. For higher energy beams, these physical interactions substantially reduce the primary beam before reaching the Bragg peak. These particles deposit dose beyond the Bragg peak and produce a so-called fragmentation tail, with the ratio of dose from fragmentation tail to bragg peak increasing with energy. Depending on the clinical scenarios for PAT, the fragmentation tail may limit the chosen arc trajectory depending on OARs in proximity to the target for higher beam energies.

Given the uncertainties in the radiobiology of arc delivery of ion beams [176], it is necessary to conduct in vitro and in vivo investigations, especially in hypoxic conditions where increasing LET using heavy ions, e.g. carbon ions, could result in an improved tumor control compared to lower LET settings. It's important to note that the ions heavier than protons, for clinically relevant energies, exhibit higher LET not just in the Bragg peak, but along the entire track. Carbon ion arcs, for example, will not only deliver a low dose bath to the patient, but also a low dose bath of increased LET_d. The radio-biological ramifications of large volumes of low doses are not well understood for heavier ions and should be thoroughly investigated. Additionally, the use of variable RBE models for proton arc therapy may prove useful in guiding clinical practice while still assuming a constant RBE. For heavier ions, mechanistic models should be further developed to enable their applicability across a wider range of dose levels, considering factors such as LET, ion species, dose-rate, tissue type, oxygen status, etc. Currently, the clinical approach does not consider end points beyond dose, LET and tissue type indicators, i.e., $(\alpha/\beta)_x$.

In conclusion, PAT cannot be evaluated solely by analyzing the physical dose distribution but must also consider potential biological effects.

Data-driven patient selection

Identifying treatment sites that would benefit most from proton arc therapy involves a nuanced approach and should involve a systematic patient selection strategy that takes into account tumor location, patient-specific characteristics, and clinical goals. Dosimetric or radiobiological improvements between IMPT, PAT or hybrid delivery may simply depend on the degrees of freedom given in the optimizer. Ultimately, once hybrid IMPT-PAT treatment delivery approaches become clinically feasible, patient selection between IMPT and PAT may no longer be necessary. The determination of the treatment delivery approach may no longer hinge on simple dosimetric differences but rather on the version of a hybrid IMPT-PAT treatment that offers greater efficiency. Recent works with photon LINACs demonstrated hybrid arcs (using IMRT and VMAT delivery in the same fraction) may present comparable delivery times with similar or better dosimetric results with respect to conventional VMAT [178,179].

That said, the incorporation of predictive models based on patient data and anatomical features could help tailor and select the treatment delivery approach prior to treatment plan. The first experience with model-based selection between photon and proton therapy of head and neck cancer patients was reported by Tambas *et al.* [180]. This model incorporates patient-specific data to guide treatment decisions, offering a promising strategy to optimize proton therapy utilization in this specific context. Building upon model-based predictions, de Jong *et al.* leverage the insights from model-based patient selection to explore the efficacy of spot-scanning proton arc therapy for oropharyngeal cancer [71]. This work demonstrates that this approach effectively reduces treatment-related toxicity in patients, highlighting the potential of proton arc therapy to enhance treatment outcomes in specific cancer cases (Fig. 9). Consequently, the fraction of oropharyngeal cancer patients benefitting from proton therapy is expected to increase in a model-based patient selection setting. Notably, the evaluation of inter-fractional robustness for $PAT_{dynamic}$ and $PAT_{step\text{-}and\text{-}shoot}$ plans for the oropharyngeal cancer patient cohort showed the potential additional need for adaptive workflows and/or strategies to promote fraction-wise target coverage [181]. Future works should address other key indications where arc therapy may provide similar benefits.

Application of LET optimization, TCP and NTCP models in future studies should be performed to reduce uncertainties and estimate the impact of arc delivery on tumor control and toxicities. Incorporating

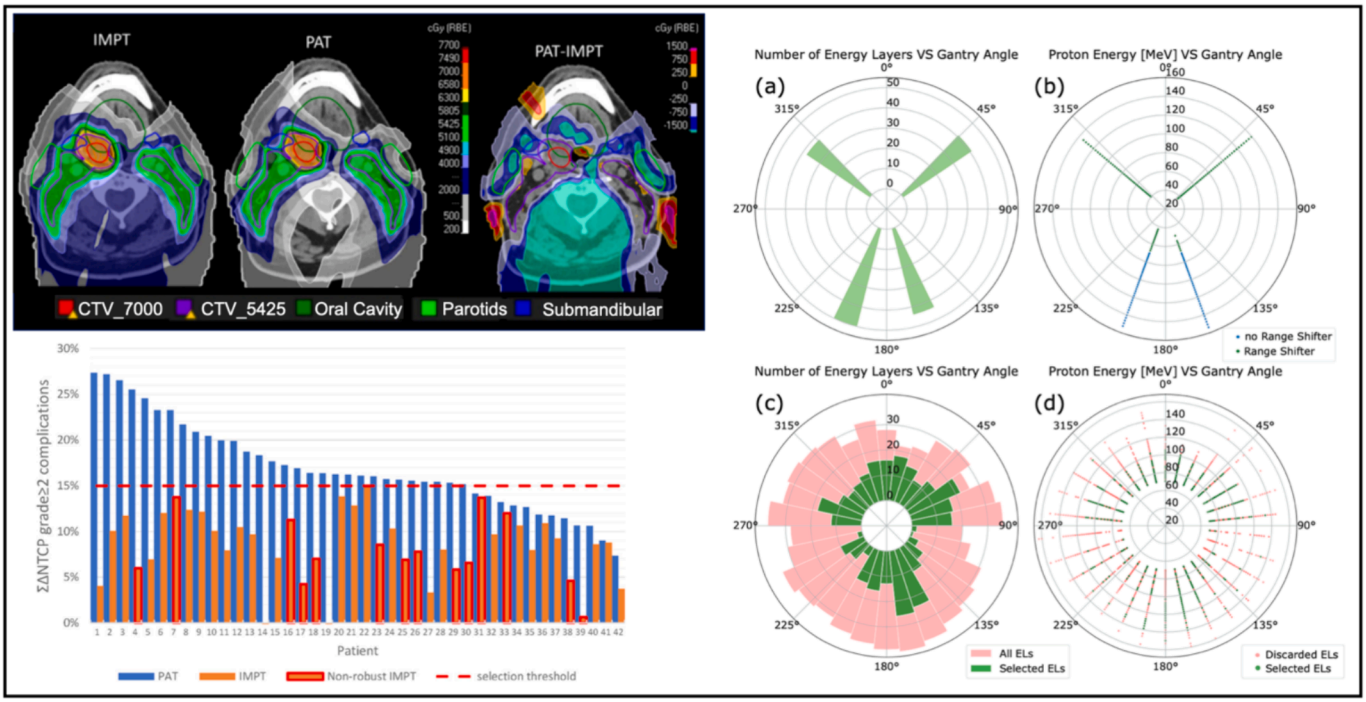

Fig. 9. Left: On top are the dose distributions of a four-beam IMPT plan and one PAT plan with 30 beams and 360 energy layers for an oropharyngeal cancer patient. The dose difference between IMPT and PAT is also shown. The bottom panel presents model-based predictions for reductions in NTCP relative to VMAT for grade-2 xerostomia and grade-2 dysphagia — IMPT (red) versus PAT (blue) plans [71,183]. Right: distribution of the number of energy layers (a, c) and proton energies (b, d) over the gantry angles in the IMPT (a, b) and the PAT plan (c, d) with all energy layers (red + green) and with 360 selected (green) energy layers [71,182]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

artificial intelligence for dose prediction assists clinical decision-making, devises robust criteria for patient selection and generates treatment plans; however, at the moment one can only speculate since such AI-driven approaches to clinical practice are in development stages. A recent review outlines how AI-powered particle therapy could improve clinical practice in terms of treatment planning, dose calculation, range and dose verification, image guidance, QA and adaptive planning [182]. Ultimately, further developments in TPS algorithms and optimization techniques dedicated to arc are needed (see section 1 on planning) in conjunction with LET optimization, TCP/NTCP and more advanced radio-biological modeling.

Motion management

One of the major challenges for all PBS techniques (extracranially) is handling the interplay effects between the beam delivery and intra-fraction motion of the patient, e.g., breathing, heart beating, abdominal muscle contraction, residual motion during breath hold, etc. Rescanning is a common motion management technique for particle therapy, which involves dividing the MUs per beam and delivering the energy layer spot sequence several times to reach the fully prescribed dose. With PBS delivery systems, there are two major types of rescanning: *volumetric* and *layer* rescanning. Volumetric rescanning is executed by cycling the entire beam multiple times over the target volume, e.g., delivering the same field twice (each sub-field with half of the MUs of the original plan). Layer rescanning involves delivering all spots for each energy layer multiple times before switching to the next energy. Rescanning can be used with free-breathing treatment techniques without the need for real-time monitoring of the tumor or the patient's breathing pattern [184]. Similarly for PAT, as with IMPT, repainting of control points may be necessary to address intra-fractional motion, maintaining dose accuracy throughout the treatment arc. However, a direct translation of existing rescanning techniques may not be warranted Implementing re-scanning techniques during $PAT_{dynamic}$ could be very different from IMPT as the gantry/PPS will continuously rotate. However, a practical solution could involve re-painting as performed in IMPT however instead through the use of multiple arcs which could be considered equivalent to two or three volumetric repainting cycles in IMPT. On the other hand, novel delivery techniques like PAT may ultimately lead to redesigned versions of existing motion mitigation techniques.

Recent studies have investigated 4D interplay effects for lung SBRT [54] and breast [55] using proton arcs (Fig. 10), which can be mitigated without applying rescanning. The accumulated dynamic 4D dose method was used to have the most detailed simulation of the interplay effect possible [185]. Proton arc demonstrated an acceptable level of robustness with respect to motion uncertainties, mainly number of beam directions, spots and energies making the delivery less sensitive to intra-fraction anatomy changes. Plan optimization and delivery parameters play a role in the interplay effect. This includes parameters of the applied robust optimization method, energies and spots selection and sequencing, spot size, ELST, scanning time, arc trajectory settings, avoidance regions, and use of rescanning and gating, if possible. Detailed studies are needed to understand the degree of impact of these parameters on 4D interplay effects for arc therapy.

Combating the interplay effect alone, however, does not recover the full plan quality theoretically achievable with particle therapy: at the planning stage, different positions of the target may need to be considered, either using an internal target volume with density override or by 4D robust optimization. A more advanced method would involve live tumor tracking, which is applicable in the same way for IMPT and PAT plans. Since tumor tracking in PBS systems is achieved by the scanning itself, no specific infrastructure would be required. Still, due to the range variations, lateral tumor tracking alone cannot fully recover IMPT plan quality either. Recent works point toward the need to combine tracking with 4D optimization [186,187]. Several 4D optimization and delivery strategies are available in the context of IMPT [188–191], but applying these strategies to PAT will be highly challenging. The uncertain

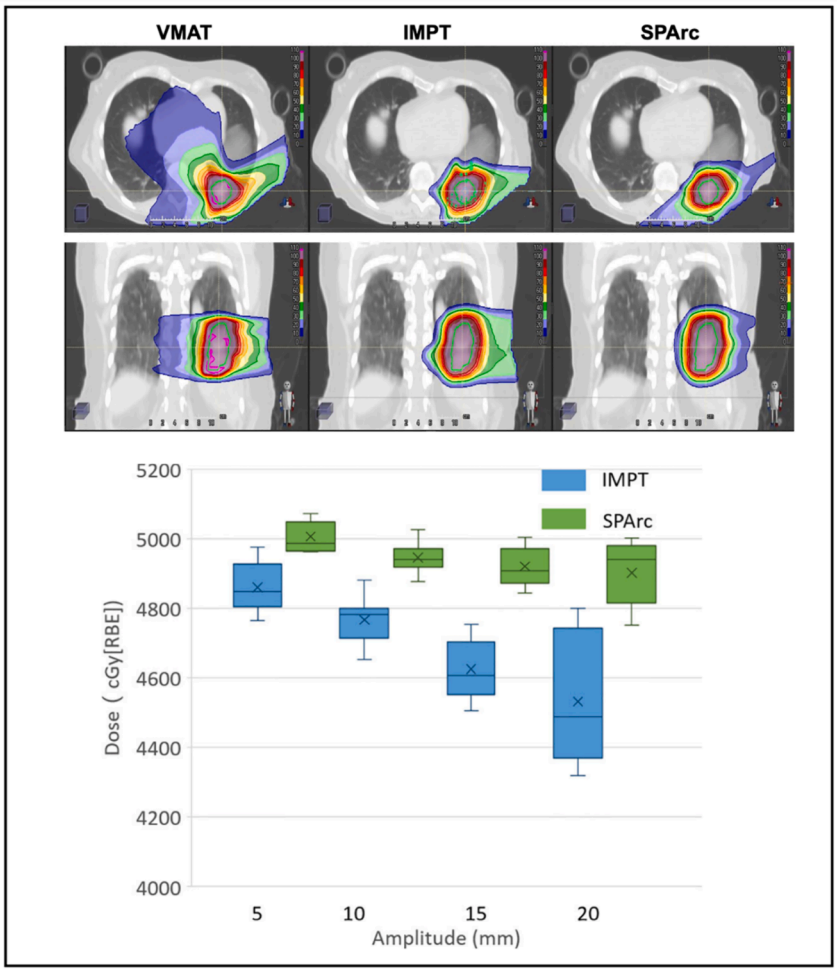

Fig. 10. VMAT and IMPT versus proton arc therapy (SPArc) for treatment of disease within the thorax, demonstrating improved conformity, reductions in the low-dose bath and changes in target D_{99} in relationship with various motion amplitudes, understanding the interplay with intra-fraction motion [53,54].

parameters of the PAT delivery, the intense computational demand of robust 4D optimization in addition to the challenges described in section 1.4, as well as the constraints posed by the energy selection strategy, will require more focused investigation.

The impact of inter-fraction anatomical changes and adaptive planning has not yet been fully investigated in the context of PAT. The work from de Jong *et al.* highlighted the level of conformity and OAR sparing that SPArc can be superior to conventional static-field MFO [71]. The use of highly conformal delivery techniques in clinical cases with higher probability of anatomy changes between fractions (H&N, prostate, nasal cavities etc.) may further justify the robust optimization and motion mitigation techniques in the clinical application.

Synergies with future modalities: hypo-fractionation, FLASH & mini-beam

As discussed in previous sections, PAT offers unique advantages over IMPT, including improved delivery efficiency, increased robustness against intra-fractional motion [42,54], and the ability to perform radiobiological dose escalation to the central region of the tumor [8,12,58,59]. These advantages make PAT particularly attractive for stereotactic procedures such as stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT). The goal of ultra-hypofractionated treatments such as SRS/SBRT is to deliver ablative doses to the central region of solid tumors or lymph nodes with very little tolerance for margins, setup and motion. Improved efficiency means faster treatment and potentially less probability of large body or organ motion. Increased robustness against motion affords increased certainty about the location and distribution of the high dose and how much dose each nearby organ receives. This may allow clinicians to potentially reduce toxicity and the ability to increase cell killing within the central region of the target, potentially affording further dose escalation and enhanced ablative effects in certain indications. Ultra-hypofractionation of $>$ 50 Gy single-fraction carbon ion therapy has been demonstrated in colorectal [192] and lung cancer [193,194] with acceptable efficacy and tolerability. For proton therapy, 15 Gy single-fraction SRS was investigated for arteriovenous malformations; however, compared to VMAT, clinical investigations and data on hypofractionation in particle therapy are sparse. Recent reviews discuss the rationale and clinical directions for hypofractionated particle therapy using ion beams but do not discuss the role of advanced delivery strategies to effectively increase the therapeutic ratio such as PAT, uHDR, spatial fractionation, etc. [195,196]. Hypofractionation has been proposed using proton arcs for lung SBRT [54], single lesion SRS [197] and single *iso*-center SRS for multiple brain metastases [198]. However, additional simulation and experimental studies should be performed to understand the feasibility and efficacy of hypofractionated PAT. In short, SBRT/SRS uses protons by allowing for faster, safer, and more biologically effective treatment delivery.

There are currently multiple competing advancements in novel delivery strategies unfolding [199], each introducing its own disruptive potential. Interestingly, there is opportunity for these developments to harmonize well together, forming a synergistic compatibility in patient-specific and biologically driven treatment design. A recent review explores prospective solutions to address existing limitations of current

clinical proton therapy by using various strategies individually or in combination, noting that some proposals, like combining arc, FLASH dose-rates and mini-beams [200], could be simultaneously disruptive and synergistic [201]. One study demonstrated that advanced delivery techniques like arc-shoot-through were required to achieve FLASH-compatible dose rates [202]. While hybrid delivery strategies might sound somewhat futuristic, several works present proof-of-concept studies which highlight the potential for hybrid approaches to further widen the therapeutic window for radio-resistant tumors, e.g., mini-beam + arc [203] and FLASH+arc [204].

Challenges in practical implementation and clinical workflow

Introducing PAT into the clinical setting may offer improved treatment delivery efficiency at the expense of, to some extent, increasing the complexity of treatment delivery, which should raise questions regarding the adaptation of clinical workflows and practical procedures. Beyond topics discussed in prior sections regarding needs specific to PAT, other clinical considerations include the dynamically rotating beam shooting through the treatment couch or support structures to increase safety and robustness (as well as through metallic implants, anesthesia masks in pediatric patients, and other similar devices), the necessity of delineating avoidance sectors to protect critical structures, and the debated role of range shifters. Although recent research suggests that range shifters may be unnecessary for several clinical treatments for PAT due to advanced beam control, their use cannot be entirely dismissed, especially for treating large superficial targets where a uniform dose distribution is challenging to achieve without them [126,143]. Moreover, planning for PAT introduces additional complexity which would benefit from automation to make the process feasible and efficient, as seen with planning automation advances in the VMAT where dedicated algorithms and internal scripting may streamline the planning process. At this time, adaptation of similar technologies to PAT may not be as straightforward due to the unique physical and biological properties of particle beams and, most of all, the current absence of clinical experience with PAT. The complexity of PAT extends beyond the technical and into the operational, e.g., the expertise needed to design, execute, and monitor PAT treatments will require dedicated investment in training and personnel, at least in the implementation phase. These considerations highlight the delicate balance between advancing treatment capabilities and maintaining practicality in clinical operations.

Impact on clinical operations and financial outlook

Particle therapy often involves longer patient in-room times compared to IMRT/VMAT, often taking 25–40 min per fraction [205]. Consequently, only a small portion of eligible patients receive this treatment due to financial constraints and limited referrals, leading particle therapy centers to either reach maximum capacity or face financial challenges. Improving cost-effectiveness is crucial for more widespread availability of particle therapy.

Although PAT is still pre-clinical, projections for increasing revenue are promising, i.e., by attracting more patient referrals due to the improved distribution, faster treatments and better patient outcomes potentially offered by arc therapy. Solutions to potentially reduce capital costs of particle therapy include enhancing patient throughput by implementing alternative setup methods like upright chair solutions and reducing fraction delivery time using more efficient techniques like arc. For instance, studies by the Beaumont group project ~ 30 % reduction in delivery time compared to IMPT, which is particularly advantageous for multi-field treatments [28]. Despite these projections, delivery times for PAT are still not well established or understood — further data on machine-specific PAT delivery times compared to IMPT for various sites are urgently needed. Additionally, boosting revenues can be achieved by attracting more patient referrals due to the improved dose distribution and better patient outcomes offered by PAT. Other means of decreasing costs are beyond the scope of this review but, in short, could involve expediting building construction, compact facility/accelerator/delivery system design, and automating planning. Again, it is important to note that since PAT is still in the experimental phase and lacks actual patient treatment data, assessments of its clinical and financial implications are currently based on hypothetical projections from pre-clinical studies [143,206].

Closing remarks

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PAT using protons and other ions species is an emerging clinical technology with the potential to improve four major aspects in clinical practice: conformity, efficiency, efficacy and robustness. Advancements in radiation treatment technology, such as arc, may improve the quality of care, minimize investment and operational expenses and increase daily treatment throughput associated with proton therapy systems. That said, several research and development initiatives are required prior to making arc delivery with ion beams a clinical reality, in terms of treatment planning, delivery, dosimetry/QA, radiobiology, and clinical direction:

Treatment planning: PAT using proton and other ion beams holds promise as a radiotherapy technique with potential advantages in dose distribution, LET redistribution, biological effects and overall treatment workflow. However, to realize its clinical potential, optimization algorithms must address plan quality, delivery time, and computational efficiency. Developing an efficient PAT optimizer that effectively utilizes the increased degrees of freedom distributions and robustness while optimizing for an efficient sequence of spots and energy layers is critical. The TPS optimization and plan generation algorithms may need to consider machine-specific characteristics in the BDT and sequence modeling for dynamic delivery. Future research will need to concentrate on enhancing optimization methods, systematically assessing the clinical impact of arc, and establishing a benchmark of the value of PAT over IMPT for certain tumor sites.

Treatment Delivery: There are two main approaches and avenues for developing the technical capabilities of rotational motion for $PAT_{dynamic}$ and $PAT_{step\text{-}and\text{-}shoot}$:

I. Gantry-based systems, including both traditional, compact and super-conducting gantry systems.
II. Gantry-less systems, including treatment chairs and upright positioners coupled with a fixed-beam nozzles, and/or other beam rotational/steering technologies.

In terms of hardware development, faster spot scanning and energy layer switching techniques are under development to continue improving the treatment efficiency of both $PAT_{dynamic}$ and $PAT_{step\text{-}and\text{-}shoot}$. Since the dynamically rotating gantry and PPS are still under development and/or in the regulatory clearance stage, step-and-shoot approaches may serve as an interim solution.

Commissioning standards and guidelines for novel delivery techniques like PAT are required to ensure safe and precise clinical implementation. Future advancements require thorough investigation and validation of proposed procedures, e.g., utilizing treatment machine log files for dose reconstruction and leveraging dosimetry equipment synchronization during $PAT_{dynamic}$ to establish robust and standardized acceptance, commissioning, and QA protocols.

Clinical outlook: Site-specific studies comparing PAT and IMPT have demonstrated improved conformity, OAR sparing, and potential reductions in treatment time and integral dose. That said, this new approach to particle therapy delivery cannot be evaluated solely by analyzing the dose distribution. We must address both physical and biological robustness against uncertainties and interplay effects, which requires establishing advanced optimization methods and radiobiological models. Investigations are needed to understand radiobiological

implications of PAT, e.g., assessing integral dose distribution, dose delivery duration, LET distribution changes, and low dose hypersensitivity to enhance treatment planning. Studies should focus on RBE variations, LET-based optimization, distributions, and predicted impact on treatment outcomes. While PAT using higher LET particles like carbon ions could provide more biologically robust treatment due to reduced dependency on biological factors, these effects need characterization and validation in vitro and in vivo, particularly in hypoxic conditions, and testing mechanistic models for arc considering LET, dose-rate, tissue type, and oxygen levels.

Effectively managing uncertainties is crucial in particle arc therapy treatment planning. Systematic range and setup errors can be incorporated in a robust optimization approach as for IMPT. For intra-fraction motion targeted investigations into motion mitigation strategies and the impact of planning optimization and delivery parameters on interplay effects are required. Robustness of highly conformal techniques like PAT against anatomical changes between fractions remains to be fully investigated.

Furthermore, we need to understand which patient populations and indications will benefit most from arc in place of IMPT delivery techniques, for example, by applying model-based patient selection strategies and predicting clinical outcomes. The potential advantages of PAT as detailed in this report are certainly laudable, but do they bring the same magnitude of advantage as the move from fixed field IMRT to VMAT in photon therapy? This remains to be seen; however, in fairly comparing such developments to IMPT, it is important that all aspects of the treatments are compared. For instance, given the degeneracy in the definition and selection of beam angles for IMPT, are we sure that particle arc treatments cannot be emulated with fixed beam techniques? Are the proposed advantages of treatment efficiency with arc competitive with other methods for making PBS more efficient (i.e., spot reduction methods)? And finally, do the modest increases in average LET in the target volume resulting from full or partial arc proton treatments (a few keV/micrometer) [8] outweigh the inevitable increase in low-dose bath resulting from these techniques compared to IMPT?

PAT is still in its infancy in the pre-clinical investigation, and its full potential is likely still to be fully exploited. Given the fundamental differences in single field dose distributions between PBS particle therapy and photons, and parallel developments taking place in IMPT (mini-beam, FLASH, etc.), particle arc may face some opposition as the delivery modality of choice in many indications for proton therapy. In parallel, PAT has the potential for hypofractionated treatments, enabling efficient, robust, and biologically effective delivery to central tumor regions, while emerging delivery strategies offer potential for synergistic treatment design to address limitations and widen the therapeutic window for radio-resistant tumors.

In summary

Particle arc therapy could be a promising clinical tool and as development continues, further site-specific studies are needed to understand where it can make the greatest impact. It is undoubtedly useful to increase the available treatment strategies for treating certain tumor types and geometries, and for one which yet again exploits the degeneracy of PBS particle therapy.

CRediT authorship contribution statement

Stewart Mein: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Sophie Wuyckens:** Writing – review & editing, Writing – original draft, Resources. **Xiaoqiang Li:** Writing – review & editing, Writing – original draft. **Stefan Both:** Writing – review & editing, Writing – original draft. **Alejandro Carabe:** Writing – review & editing, Writing – original draft. **Macarena Chocan Vera:** Writing – review & editing, Writing – original draft. **Erik Engwall:** Writing – review & editing, Writing – original draft. **Fracchiolla Francesco:** Writing – review & editing, Writing – original draft. **Christian Graeff:** Writing – review & editing, Writing – original draft. **Wenbo Gu:** Writing – review & editing, Writing – original draft. **Liu Hong:** Writing – review & editing, Writing – original draft. **Taku Inaniwa:** Writing – review & editing, Writing – original draft. **Guillaume Janssens:** Writing – review & editing, Writing – original draft. **Bas de Jong:** Writing – review & editing, Writing – original draft. **Taoran Li:** Writing – review & editing, Writing – original draft. **Xiaoying Liang:** Writing – review & editing, Writing – original draft. **Gang Liu:** Writing – review & editing, Writing – original draft. **Antony Lomax:** Writing – review & editing, Writing – original draft. **Thomas Mackie:** Writing – review & editing, Writing – original draft. **Andrea Mairani:** Writing – review & editing, Writing – original draft. **Alejandro Mazal:** Writing – review & editing, Writing – original draft. **Konrad P. Nesteruk:** Writing – review & editing, Writing – original draft. **Harald Paganetti:** Writing – review & editing, Writing – original draft. **Juan María Pérez Moreno:** Writing – review & editing, Writing – original draft. **Niek Schreuder:** Writing – review & editing, Writing – original draft. **Martin Soukup:** Writing – review & editing, Writing – original draft. **Sodai Tanaka:** Writing – review & editing, Writing – original draft. **Thomas Tessonnier:** Writing – review & editing, Writing – original draft. **Lennart Volz:** Writing – review & editing, Writing – original draft. **Lewei Zhao:** Writing – review & editing, Writing – original draft. **Xuanfeng Ding:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

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Appendix A. Supplementary data

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