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Review paper

Clinical practice vs. state-of-the-art research and future visions: Report on the 4D treatment planning workshop for particle therapy – Edition 2018 and 2019

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ABSTRACT

The 4D Treatment Planning Workshop for Particle Therapy, a workshop dedicated to the treatment of moving targets with scanned particle beams, started in 2009 and since then has been organized annually. The mission of the workshop is to create an informal ground for clinical medical physicists, medical physics researchers and medical doctors interested in the development of the 4D technology, protocols and their translation into clinical practice. The 10th and 11th editions of the workshop took place in Sapporo, Japan in 2018 and Krakow, Poland in 2019, respectively.

This review report from the Sapporo and Krakow workshops is structured in two parts, according to the workshop programs. The first part comprises clinicians and physicists review of the status of 4D clinical implementations. Corresponding talks were given by speakers from five centers around the world: Maastro Clinic (The Netherlands), University Medical Center Groningen (The Netherlands), MD Anderson Cancer Center (United States), University of Pennsylvania (United States) and The Proton Beam Therapy Center of Hokkaido University Hospital (Japan). The second part is dedicated to novelties in 4D research, i.e. motion modelling, artificial intelligence and new technologies which are currently being investigated in the radiotherapy field.

1. Introduction

To date, proton therapy has been widely demonstrated to be an advantageous approach to treat cancer patients in comparison to other radiotherapy modalities in terms of target dose conformity and possible decrease of the dose to surrounding tissues [1–5]. Proton therapy enables a reduction of side effects while maintaining identical tumor control as with photon therapy. However, its high precision raises questions about the safe use of scanning proton beams for treatment of moving targets due to, e.g. sharp end-of-range or the presence of scanning dynamics.

The clinical interest and research activities, which started around a decade ago, enabled first clinical implementations of 4D particle therapy. Over the past 10 years, the participants of the annual 4D workshops

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for particle therapy reported on research advancements in motion imaging, monitoring and modelling as well as on research related to 4D treatment planning and delivery, 4D quality assurance and 4D dosimetry [6–10]. The clinical translation of research outcomes in the field of 4D particle therapy remains the key component needed for safe clinical 4D treatments.

The 4D Treatment Planning Workshop for Particle Therapy has been held annually since 2009 providing an informal platform to discuss current clinical implementations, research approaches and future perspectives of 4D particle therapy. Since the first edition, the scope of the workshop has expanded significantly, starting from truly research aspects and currently discussing the clinical implementations of 4D particle therapy. In 2018 the 10th edition took place in Sapporo, Japan. The Proton Beam Therapy Center of Hokkaido University Hospital started clinical operation in 2014. In 2019 the 11th edition of the 4D workshop took place in Krakow, Poland at the Institute of Nuclear Physics PAN, part of which is Cyclotron Centre Bronowice, the first operating proton therapy site in Poland offering ocular melanoma treatments from 2011 and proton therapy for other, deep situated indications from 2016. Total number of participants of the Krakow workshop exceeded 65 people from 35 centers and 12 countries. The program of the meeting, as opposed to previous editions of the workshop, was divided into two major parts: first day of the workshop focused on examples of clinical applications of 4D particle therapy, while the second was fully dedicated to research advances in the field. In this report we present topics that were brought up during the 2018 and 2019 workshop sessions to summarize the state-of-the-art of 4D particle treatments and arising advancements that might shape the future of 4D particle therapy.

Section 2 of this report focuses on an overview of 4D solutions currently implemented in the clinical practice (e.g. in Europe (University Medical Center Groningen, Maastro Clinic), the United States (MD Anderson Cancer Center, University of Pennsylvania) and Japan (Hokkaido University)), presented by clinicians and clinical medical physicists during the 2018 and 2019 workshops. Section 3 reports on novelties in 4D imaging, e.g. in-room imaging capabilities, motion modelling and artificial intelligence approaches in 4D data processing presented by speakers from Europe (Ludwig-Maximilians-Universität München, University College London, University of Manchester, University Medical Center Groningen, Paul Scherrer Institute) and the United States (Emory University). It also covers biology aspects to be considered for 4D particle therapy, e.g. effects of inhomogeneous fraction dose or developments towards ARC and FLASH treatment approaches. In Section 4, it summarizes consortia and committees dedicated to the topic of 4D particle therapy, such as EPTN, PTCOG or RAPTOR. In the following report we restricted ourselves to include mainly the literature review of the last five years. It is also a continuation of 4D workshop reports series, which has started in 2010. Since then, five reports were published by workshop organizers and participants, summarizing the meetings and the status of 4D treatments implementation [6–10].

The program of the 4D workshop encompasses usually 12 invited talks, each with a dedicated discussion slot. Researchers are given the opportunity to contribute to the workshop during the poster session. In 2018, as well as 2019, approximately 12 posters were selected for presentation, covering a wide range of topics. In 2018 the three best abstracts, related to "First steps towards a 4D Cone-beam CT reconstruction workflow for moving targets at a scanned proton gantry system" (Lydia den Otter, UMCG, The Netherlands) [11], "Respiratory-gated carbon-ion beam treatments of abdominal targets at CNAO: clinical introduction of 4DMRI motion analysis" (Alessandro Vai, CNAO, Italy), "Both four-dimensional computed tomography and four-dimensional cone beam computed tomography under-predict lung target motion during radiotherapy" (Elisabeth Steiner, ACRF Image X Institute, The University of Sydney Central Clinical School, Australia) [12] were awarded with travel grants. The best awarded poster in 2019 was "Validation of 4D accumulated dose at a proton therapy CBCT scanner using MA-ROOSTER and a porcine lung phantom" (first author: David Bondesson, presented by Christopher Kurz, LMU Munich, Germany) [13].

2. Clinical implementations of 4D particle therapy

Despite a lot of practical difficulties related to 4D particle therapy implementation, including hurdles in patient selection procedures and following 4D planning and delivery strategies, many centers already started 4D clinical operation in the last years. Due to the very few guidelines [14] and lack of comprehensive commercial solutions for 4D treatments, 4D clinical protocols presented during the workshop varied across the institutions, depending on the center-specific experience and the treatment indication. The format of the 4D workshop, which encourages to share the knowledge among centers performing 4D treatments or being at different stages of 4D particle therapy implementation, is a valuable approach to further standardize the treatment of moving targets. Below, we summarize in a comprehensive overview 4D proton therapy treatment strategies, which are already implemented clinically, as they were presented during the Krakow and Sapporo workshops 2019 and 2018, respectively.

a. Patient selection based on indication, clinical gain and motion amplitude

Spatial and temporal changes in position of thoracic and abdomen tumors are mostly the effect of breathing and, to a lesser degree, cardiac and peristalsis activity [15]. To date, many studies have been dedicated to the evaluation of the dosimetric impact of respiratory motion [16–19]. Indications such as, e.g. lung or liver, have been treated for several years with stereotactic body radiation therapy (SBRT) or passively scattered particle beams [9]. Recently, when active scanned proton pencil beam technique became more accessible and affordable, the developed 4D solutions needed to be revised or improved to fully exploit the precision of scanned proton beams characteristics and to address possible dosimetric consequences of the interplay effect [10]. The advancement in pencil beam scanned proton therapy (PBS-PT) was followed by the progressive technical development of 4D tools, which enabled the clinical transition for various indications prone to the movement. Nowadays, the spectrum of clinical indications has substantially increased over the last years beyond breast, lung and liver, which was reflected in the talks of the Krakow and Sapporo 4D workshops. Speakers presented their approaches to treat also lymphoma, thymoma, esophagus and pancreas. Also the prostate was presented as a 4D indication, which is affected, e.g. by peristalsis activity or bladder filling, but not by the respiratory motion itself. The wide range of new 4D indications depicts the extensive work which has been done over the last years in all centers. Some of the results and implemented solutions for specific indications have been already published [20–22].

The patient selection for a specific 4D treatment protocol is complex and the consideration of motion in the qualification procedure is indispensable. In the case of 4D particle therapy, the profound analysis of risks and benefits associated with the physical properties and radiobiological effectiveness of particles is essential [5]. Resulting treatment decisions are based on the evaluation of both physicians and physicists for each patient case individually. The expected clinical gain and the motion characteristics of a specific patient are only some of the variables, which are necessary to be considered.

Even though proton therapy has become more available in recent years, the technical charge remained higher in comparison to photon radiotherapy. The cost-effectiveness of more sophisticated techniques should be critically verified, which is inevitably connected with the establishment of insurance coverage. Basically, reliable and evidence-based clinical gain needs to be provided. Durante et al. presented difficulties in the introduction of randomized clinical trials (RCT) for proton therapy and underlined their importance in evaluation of the clinical benefit [5]. Although several RCTs are currently ongoing around the world, the necessity of long-term follow up of tumor progression and side effects limits the feasibility of their use in rapid technological evolution of 4D proton therapy. The model-based approach is an alternative method of defining which patients would receive the greatest clinical gain from selected therapy [23–24]. It is based on comparative evaluations of photon and proton plans with regard to radiation toxicity predicted by normal tissue complication probability (NTCP) models. Dose differences to organs at risk (OAR) are translated into corresponding NTCP values, yielding in a delta NTCP, which estimates the clinical gain of one approach over the other. Following achieved delta NTCP value and with regard to the severity of complication, the patients are referred to the suitable treatment option, accordingly to the nationally agreed consensus of acceptance [23,25]. Teoh et al. presented a model-based approach for a patient cohort with locally advanced lung cancer [26]. They concluded that patients with previous pre-existing heart disease would show the greatest benefit from using an intensity modulated proton therapy (IMPT) over volumetric modulated arc photon therapy (VMAT).

For 4D indications, the premises for informed patient selection is 4D imaging. 4D imaging is required for motion qualification and the decision on a specific 4D treatment strategy [9]. A thorough motion analysis should also include estimation of motion variations associated with specific tumor types in terms of size and location [27]. The possible correlations between target movement and external signal acquired from motion surrogate, i.e. thorax surface, should also be considered at this stage of treatment preparation. All mentioned factors are intended to enable the subsequent patient qualification to certain 4D treatment approach and supporting motion mitigation techniques. According to the consensus guidelines issued by PTCOG Thoracic and Lymphoma Subcommittee [14], each institution needs to establish its own criteria for tumor motion threshold. The threshold value is based on measurements performed according to the guidelines, i.e. for different target and motion scenarios and under various delivery conditions. Therefore, clinically applied motion thresholds are highly center-specific and based on the technical properties of each delivery system individually. It was reflected in the talks presented in the clinical sessions of the 4D workshop, which showed that each center implemented its own strategy to address 4D particle therapy treatments.

b. Selection of motion monitoring and mitigation approach

Motion management methods are required to control, limit and take into consideration inter- and intra-fractional anatomical changes [28]. Adequate choice of individual patient immobilization and motion monitoring device is the subsequent stage of the 4D treatment preparation and plays an important role in minimizing the deterioration of 4D dose distribution due to breathing. A motion mitigation solution, whose purpose is to minimize the negative dosimetric effect of motion, could be applied either in the form of an active or passive management method, or additional immobilization accessories and planning approaches, based on the profound analysis of each patient motion. Usually, a motion mitigation method is used, when tumor motion amplitude exceeds a specific threshold [6].

In case the motion amplitude does not exceed a certain threshold, typically a passive management of motion is applied, either in the form of rescanning [7] or in the form of margins added to the target volume to encompass the possible tumor locations [29]. Rescanning refers to the delivery of dose spots in multiple iterations in order to smooth out the dose inhomogeneities resulting from the interplay effect [14]. Prospective 4D dose evaluations can be performed to estimate the dosimetric impact of dose blurring and the interplay effect, potentially triggering the requirement of additional motion mitigation techniques [21,30]. See, e.g. Gelover et al. for indication-specific motion management guidelines for liver and breast/chest wall treatments [31].

In some 4D cases, where the tumor amplitude exceeds a facility specific motion thresholds and the use of a passive approach on its own does not sufficiently overcome detrimental effects of breathing, an active motion mitigation method, or additional devices which help to reduce the motion extent, are usually applied. During the 4D workshop in Krakow, speakers presented methods such as, e.g. breath hold, abdominal compression or gating, employing either optical surface imaging methods or fluoroscopy imaging of internal fiducial markers. Optical surface imaging, which uses external surrogates to derive the respiration signal, was presented as a motion monitoring approach often used to guide active motion mitigation approaches. The advantage of optical methods results from the ability to monitor the patient surface online without additional imaging dose [32]. However, their main limitation is often the inability of adequate mapping of the internal tumor motion, depending on the exact target location, and therefore an attention should be paid to choose the appropriate motion model describing the correspondence between internal motion and motion surrogate [28]. Different approach, employing the fluoroscopy-based real-time imaging, a basis of real-time image guided proton therapy (RGPT), has been implemented at Hokkaido University and is used in prostate, liver, pancreas and lung cases [33–34].

Voluntary breath hold and deep inspiration breath hold (DIBH, active breath holding under full inspiration) are widely used in thorax treatments, e.g. in breast treatments, because these techniques allow to increase the tumor-to-OARs distance [35]. The patient is coached to breath in and out to enable the irradiation when the thorax surface is within the defined gating window. Therefore, the breathing signal has to be monitored online over the entire course of treatment.

To obtain a more stable and reproducible breathing signal, which supports motion monitoring methods and increases the accuracy of 4D dose delivery, active breathing control solutions are often applied in clinics. As an application, Nasal High Flow Therapy (NHFT) (ARIVO ©) was mentioned during the workshop in Krakow. The NHFT system is used, e.g. for breast and lung cancer patients at Maastro Clinic. Furthermore, the SDX System ®, used at UPenn, supports breath hold (BH) treatments of gastrointestinal and lung cases. Both solutions enable the patient, through coaching, to breathe regularly and evenly (NHFT), or to hold the breath actively and in a controlled manner (SDX) in order to achieve reproducibility of successive breaths or breath holding phases. Moreover, also the High-Frequency Percussive Ventilation (HFPV) [36] approach might be used to suppress respiratory motion. The principle of the HFPV technique is the generation of intermittent, positive pressure in the lung using high-frequency, percussive pressure pulses providing gas exchange without active breathing. In 2018, Emert et al. proposed the comparison of HFPV technique and an enhanced DIBH strategy (eDIBH), which uses pre-DIBH O_2 hyperventilation to extend the breath hold duration. Although both methods were applicable and tolerated, preliminary study results, presented by a poster in 2019, suggested that eDIBH outperforms HFPV, thus demonstrating that eDIBH could provide a feasible, well-accepted, and effective suppression of respiratory motion during PBS proton therapy [37].

Other commonly used planning solution in 4D practice, mentioned in a talk by Arturs Meijers from UMCG, is the enlargement of the beam spot size which reduces influence of the motion effects on the dose distribution and results in more homogeneous dose. As pointed out in a talk by Xiaodong Zhang from MD Anderson, the delivery dynamics of spots is of high concern and the choice of optimal scanning beam direction, along the greatest extent of the tumor, might play a substantial role in the mitigation of the interplay effect. To evaluate the deterioration of the dose due to this effect, a comparison between a static and one fraction dynamic dose could be applied [16].

In summary, in order to achieve best treatment outcome under breathing conditions and due to the fact that each specific solution supporting 4D treatment has specific advantages and limited precision in different 4D scenarios depending, e.g. on treatment indication, motion monitoring techniques are often combined with mitigation solutions [8,14,28]. Many sophisticated techniques of motion monitoring and motion mitigation, both for photons and protons, were reviewed in detail in the 4D workshop report from 2016 and 2017 editions [10]. Nevertheless, the choice of methods for clinical 4D PBS treatments strongly depends on the availability of tools on site and capabilities of the particular proton facility [28,38].

c. Treatment planning
i. 4D imaging and contouring

Moving targets are one of the most difficult indications to be planned for scanned proton therapy [21,39]. Reasons are the high sensitivity of the PBS technique to treatment uncertainties, i.e. range changes, interplay effect or dose blurring, especially if respiratory motion occurs [10,40].

Any type of treatment planning in radiotherapy is based on an accurate delineation of the tumor volume and surrounding organs at risk (OAR). In case of 4D treatment planning, delineation of anatomical structures is even more challenging due to the aspect of motion and also the necessity of contouring verification within the whole respiratory cycle. In many centers, 4DCTs are used in clinical practice for contouring and planning purposes. The 4DCT is a time-resolved CT acquired in the presence of breathing motion. Based on the recorded CT data and respiratory pattern, certain breathing phases can be reconstructed and equally divided in time-percentage bins of the whole respiratory cycle. If a 4DCT is reconstructed to 10 breathing phases, then the so-called 0% phase corresponds to the maximum inhale, while the 50% phase to maximum exhale of the respiratory cycle [41]. Based on the acquired 4DCT, other 3DCT images used at the contouring and planning stages could be reconstructed, e.g. an average or maximum intensity projection (MIP), as well as mid-ventilation (MidV) CT scans [42–43]. Additional information obtained from other imaging modalities, e.g. positron emission tomography (PET) or contrast enhanced CT, are often used to support the delineation process in lung or liver cases, respectively [44–45]. Subsequently, based on modified and registered imaging data, tumor volume and OAR are contoured according to facility- and site-specific approaches.

Commonly, internal target volume (ITV) margin approaches are used in 4D treatment planning [6]. The ITV contains the union of target positions from all or selected, e.g. end-of-inhale and end-of-exhale, breathing phases obtained from 4DCT, considering the target motion extent in all directions. In combination with rescanning, the use of an ITV is commonly considered the most robust and was mentioned as clinically applied by Xiaodong Zhang from MD Anderson, Wei Zou from UPenn and Arturs Meijers from UMCG.

Apart from the above mentioned ITV definition, there are several different methods to establish motion encompassing margins based on 4D imaging, which are presented in the literature [15,46]. For example, reconstructed CT scans of maximum exhale, MIP and MidV, or a combination of both, maximum inhale and maximum exhale images, are also feasible to be used for target delineation. Reason for the use of the end of expiration scan might be associated with the fact that it is the most reproducible breathing phase within the whole respiratory cycle [47] and was mentioned by Judith van Loon from Maastro Clinic as an image which could be used for contouring purposes. As an alternative option, Wei Zou from UPenn also presented the possible combination of maximum inhale and exhale images for the creation of an ITV. Different approach, based on MIP scans, might be useful especially in lung cancer cases, where the tumor is surrounded by low-density soft tissue [48]. However, a great attention should be paid in areas where the tumor is attached to critical organs of similar density value to the tumor such as, e.g. diaphragm or chest wall, because it could result in the underestimation of treatment volume [46].

To account for random and systematic geometrical uncertainties, which are present during treatment preparation and delivery, a concept of additional safety margins surrounding the ITV is usually applied, according to the van Herk formula [49]. Regardless of the chosen delineation approach and margins, the defined volumes should be always subsequently reviewed within the whole breathing cycle to provide sufficient dose coverage to the target. That is consistent with the PTCOG Thoracic and Lymphoma Subcommittee consensus guidelines, which contain the overview of procedures for target definition and treatment simulation in case of PBS therapy for thoracic malignancies [14].

It is also worth mentioning that the European Particle Therapy Network workgroup 4 on image guided proton therapy (IGPT) issued in 2018 a survey and published the results summarizing procedures and clinically used solutions for image guidance in 12 European particle centers [50]. The questionnaire contained questions regarding imaging solutions starting from patient immobilization, through treatment planning, to the treatment verification, evaluation and possible treatment adaptation. The report shows variety across different particle therapy centers being at different stages of implementation of image guidance procedures. It is a valuable comparison of clinically used solutions, which might be helpful in creating unified consensus on IGPT treatments.

One of the last treatment preparation steps is the possible application of density overrides depending on the specific planning case. The speakers from Maastro Clinic, MD Anderson and UPenn mentioned the clinical use of this approach either to the tumor or critical organs, i.e. diaphragm, in their centers. They concluded that the density override to the target volume, historically used in passive scattering proton therapy (PSPT), might also be beneficial in an intensity modulated proton therapy (IMPT) treatment planning, providing more robust target dose coverage in different breathing phases of 4DCT. The density override applied to critical organs such as, e.g. diaphragm in esophageal cancer, was presented in the poster by Visser et al. in 2019. As it was shown, if a density override is applied, it should be always carefully analyzed in terms of dosimetric outcome for individual cases, for instance by means of dose recalculation and robustness evaluation.

Lastly, recent studies have shown the potential of 4D-MRI for target definition and tumor motion evaluation [51]. This potential future direction was reflected in the poster presented by Rabe et al. in 2019. They compared the ITV and MidV approaches using the 4D-MRI for target definition and observed higher robustness of 4D-MRI against interfractional changes in comparison to standard 4DCT imaging.

ii. Beam angles selection

A well-known feature of proton therapy is the ability to create very steep distal fall-off regions. This causes that the proton range is sensitive to any density variations occurring along the beam path [52]. Since the possible impact of these heterogeneities may substantially vary depending on the irradiation direction, careful selection of beam angles is an important step of planning. General recommendation is to choose such irradiation directions, which are "motion-robust", i.e. avoid large density gradients in the beam path, minimizing range uncertainties [14]. In practice, that means that the beam direction should be as parallel as possible to the dominating tumor motion direction and should not stop proximally to critical organs, also to minimize the uncertainties in relative biological effectiveness (RBE), which occurs at the end of proton beam range [53].

The specific beam angle selection procedures for various 4D indications were presented during the workshop by speakers from UMCG, MD Anderson and UPenn. In lung cancer cases a combination of two or, more commonly, three irradiation fields creates conformal dose distribution within the tumor and enables to decrease the dose to surrounding critical organs. For example, in tumors located in the lower lobe of the lung, posterior and posterior oblique beam directions might be combined, minimizing unwanted dose to the spinal cord and being thus more stable than beams from other directions, which was presented by Wei Zou from UPenn. For breast cancer, en-face beam(s) are commonly used, mostly because of the overlap between motion and beam angle direction. In lymphoma cases presented by Arturs Meijers from UMCG, anterior beams are primarily used with possible, additional posterior beam to cover the axillary nodes and avoid dose to breast tissue. Despite slight differences in selection of beam angles among facilities, the general rules mentioned above were consistent in all presented 4D treatment planning protocols used clinically.

iii. 3D and 4D robust optimization

The main purpose of introducing robust optimization in proton treatment plans is to account for possible 3D and 4D dose delivery uncertainties associated with, e.g. patient setup, range uncertainties, interplay effect, breathing motion, fractionation, anatomical variations or beam delivery characteristics. In photon radiotherapy, due to the depth-dose characteristic of beams, a concept of geometrical CTV-to-PTV (clinical-to-planning target volume) expansion might be sufficient only in a limited number of cases and indications to achieve dose distribution robust to photon treatment uncertainties. In case of proton beam delivery the classical ITV- and margin-based concepts are usually not satisfactory, when used individually, to account for treatment uncertainties. For PSPT or single field uniform dose (SFUD) plans, where each treatment field has homogeneous dose distribution, the employment of range adapted margins, accounting for possible range variations, might improve dosimetric results [6]. For IMPT plans, where each of the treatment fields has a heterogeneous dose distribution, it is more difficult to control detrimental effects of motion and consequent range changes. Therefore an expanded robust optimization is necessary in order to obtain clinically acceptable treatment plans.

A 3D robust optimization (3DRO) approach accounts for setup errors and range uncertainties in treatment plan optimization. The robust optimization methods, distinguished in the literature, include, e.g. voxel-wise, scenario-wise robust optimization as well as probabilistic planning approach [40]. Range uncertainties may cause detrimental effects to both, surrounding OAR and target volume itself, therefore the inclusion of range uncertainty error is extremely important to be included in the optimization process. Meijers et al. presented the assessment of range errors in a 4D porcine lung phantom with proton radiography to justify the use of 3% range uncertainty error in robust treatment planning in thoracic cases [54].

A 4D robust optimization (4DRO) technique, mentioned in a talk by Katja Langen from Emory University, was essential to be introduced to satisfy the clinical requirements accompanying the 4D proton planning implementation. The 4DRO directly allows for including the respiratory motion, because the 4D treatment plan is optimized with regard to different breathing phases of the 4DCT. According to research studies, 4D robustly optimized treatment plans are characterized by higher robustness to delivery and motion uncertainties in comparison to conventional ITV- or margin-based approaches, as well as 3DRO [55]. Ge et al. presented a comparison of the ITV method, 3DRO and an in-house developed 4DRO additionally accounting for breathing motion [40]. In all cases, the 4DRO was superior over other solutions, confirming thus the clinical potential of its use for 4D indications. Another investigation on 4DRO technique was conducted by Mastella et al. [56]. They compared two strategies of 4DRO for different number of breathing phases, i.e. ungated and gated treatment approach, which was restricted to only three breathing phases. The latter case resulted in higher robustness and normal tissue sparing in comparison to ungated 4DRO containing breathing phases from the whole respiratory cycle and thus larger motion extent.

iv. 4D evaluation and delivery

Before treatment delivery, a specific 4D plan should be evaluated regarding its robustness towards all possible occurring uncertainties [14,57]. As an example, Korevaar et al. presented a method for comparable robustness evaluation between photon and proton plans, based on the dosimetric comparison between conventional PTV and developed scenario-based approach [58].

The monitoring of anatomical changes throughout the course of fractionated treatments is essential to determine whether adaptive replanning is required. For this purpose, verification 4DCT scans or scans obtained from the daily imaging, e.g. cone beam CT (CBCT), if available, are used to review the anatomy variations with respect to the planning CT. During the workshop Wei Zou from UPenn highlighted the necessity of, e.g. bi-weekly 4DCT checks for lung and abdomen cases due to the high possibility of pleural effusion, tumor density change, atelectasis or lung reinflation during the course of treatment. The log files from treatment delivery and breathing signal recorded fraction wise, might be used for 4D dose reconstruction on weekly 4DCTs as a 4D quality assurance check of delivered dose, which was presented by Arturs Meijers from UMCG [21,22] as well as addressed by others [59].

An increased use of CBCT imaging and the clinical implementation of 4D-CBCT imaging during proton therapy could help to more accurately monitor motion variations or weight gain/loss, and might be recommended as a daily imaging modality for 4D indications. However, further developments of 4D reconstructions of CBCTs in the context of protons are needed, which is also linked to less projection data available in proton therapy due to the limited accessibility to CBCT technique in proton centers. An example of 4D-CBCT reconstruction from 3D-CBCT data, using the MA-ROOSTER method (Motion-Aware ReconstructiOn method using Spatial and Temporal Regularization), was presented in a poster by den Otter et al. in 2018 and recently published [11]. Sound dosimetric evaluations for protons still require CT images, at least in 4D indications, since the compromised quality of CBCT images impairs the proton dose calculation accuracy. Future development and improvements in CBCT based synthetic CT generation might help to overcome this current limitation [60].

3. Novelties in the 4D particle therapy research

The following section is mostly related to aspects of 4D particle therapy treatments that are not clinically implemented yet. We comment on the progress in research related to motion imaging, modelling and monitoring, and we include a discussion on applications of artificial intelligence (AI) methods for particle therapy of moving targets, as they were newly addressed during the workshops in Sapporo and Krakow. Moreover, we address the future challenges and vision for development of 4D particle therapy, linked to new trends in radiation biology and development of new technology, as for example application of high dose rates (FLASH effect) or rotational irradiation methods (ARC) in particle therapy.

a. 4D imaging for motion modelling and monitoring

As highlighted in previous sections, the component of characterizing tumor motion cannot be neglected when treating 4D indications and the acquisition of respiratory pattern forms a basis for motion monitoring prior and during the treatment delivery. Additionally, during the course of treatment, motion checks based on 4D images are recommended to evaluate possible deviations from the planning assumptions. However, the advantages of continuous 4D imaging have to be weighted against the exposure of normal tissue to imaging dose. For this reason, other imaging methods administering low or no dose to patient are developed to provide true information on patient/tumor motion. In addition, motion models equipped with motion characteristics obtained from a surrogate signal could be used to predict intra-treatment motion of radiotherapy target and to retrospectively or adaptively evaluate dose distribution administrated to the patient during the treatment.

Both 4D workshops, in Krakow and in Sapporo, included review talks on imaging methods that can be applied in the treatment room to acquire and monitor motion information needed for 4D therapy planning and delivery. The clinical applicability of 1D, 2D, 3D and 4D systems providing information based on patient surface (external surrogate) or internal anatomy motion were reviewed by Marco Riboldi from LMU Munich in Krakow and Naoki Miyamoto from Hokkaido University in Sapporo. External 1D systems like spirometry, pressure sensor or laser distance measurement do not administer additional dose to the patient and, even if they have limited precision accounting only for one motion direction, if 2D and 3D methods are not available on site, might be considered as the solutions supporting motion monitoring during, e.g. gated irradiation. Optical or electromagnetic (EM) systems, which are capable of tracking the patient surface or the position of the markers placed at the thorax, can provide the external 3D information [32]. The advantage of these methods is high, sub-millimeter accuracy, although the proximity of EM generator to the CT scanner or the gantry motion itself might distort the tracking and preclude its clinical use during 4DCT acquisition and delivery. The electromagnetic tracking systems can also provide 3D information on the internal anatomy motion using transponders implanted in the patient. The motion of the internal anatomy is also frequently obtained from imaging of the implanted fiducial markers using 2D, X-ray based orthogonal fluoroscopy imaging systems. Recently, also markerless fluoroscopy-based tumor tracking was proposed [61]. During the Sapporo workshop, Toshiyuki Terunuma from University of Tsukuba, presented a personalized deep learning method for real-time projection of CTV contours utilizing X-ray fluoroscopy. Fluoroscopy based tumor tracking, even if simple to be applied using in-room X-ray imaging equipment, is intrinsically limited by the fluoroscopy image quality, 2D acquisition mode and relatively high imaging dose.

Currently, the most complete information on motion can be obtained in-room, either from kV CT installed on-rails or from kV Cone Beam (CBCT) installed on gantry, gantry nozzle, separate robotic arm or on treatment couch [62]. Both, on-rail and CBCT approaches are widely investigated and recently, CBCT scanners are installed in the newly designed proton therapy treatment rooms. The in-room installation of 3D imaging has great potential for image guided adapted treatment as it was discussed by Paul Keall from Sydney Medical School and proposed for instance by Kurz et al. [63]. In-room CT can be also utilized for offline guidance of the treatment of moving targets as discussed in Sapporo by Shinichiro Mori from National Institute of Radiology Science. Recently, Bryce-Atkinson et al. presented the use of respiration correlated cone-beam CT (4D-CBCT) in lung cancer patients [64]. 4D-CBCT allows for accurate tumor localization because of the consideration of respiratory motion, however, the acquisition is longer than in conventional 3D-CBCT modality and requires sorting of images into the following breathing phases. The reduction of scan time below 2 min showed significant degradation of image quality. The resulting limited 4D-CBCT image quality [64] was the reason for multicenter study on CBCT image reconstruction algorithms aiming at the reduction of imaging dose and image acquisition time [65]. X-ray based, in room 4D imaging has currently the potential to provide the most comprehensive 4D information needed in the clinical routine, but can be applied, only, if the administration of the imaging dose would be considered clinically acceptable.

The advantage from clinical application of in-room X-ray based 3D and 4D imaging methods led to attempts of incorporating also other in-room imaging methods such as Ultrasound (US) or Magnetic Resonance Imaging (MRI), which do not administer ionizing radiation to the patient. Ultrasound has been already widely investigated for imaging of abdominal organ motion. Recently, a new approach to optimize the position of the robotic arm holding the ultrasound probe to avoid collisions between the therapeutic beam and the robotic arm was investigated by Schlüter et al. [66]. MRI offers radiation-free images with high-resolution and superb soft tissue contrast that can be utilized for radiotherapy treatment planning and motion management [67,68]. The incorporation of MRI in photon treatment room for image guidance, i.e. MRI-LINAC, was addressed in a dedicated talk by Bas Raaymakers from University Medical Center Utrecht during the workshop in Sapporo. In Krakow, Marco Riboldi from LMU Munich addressed limitations of MRI spatio-temporal resolution and reviewed 3D image reconstruction method for MRI-guided treatments exploiting 2D orthogonal cine-MRI slices [69]. Important application of 4D-MRI imaging to build a motion vector field applied to treatment planning CT, subsequently used for plan re-optimization/adaptation, was recalled by Anthony Lomax from PSI.

One limitation of the majority of current 4D imaging methods is that they assume reproducible motion, and hence cannot account for inter- or intra-fractional changes to the motion. Motion models have been proposed for a wide range of different types of motion, including intra-fraction motion such as respiration [70] and cardiac motion, and inter-fraction motion such as setup errors and anatomical variations. Such motion models might be used for motion compensation during imaging or treatment planning and delivery, which was highlighted in the previous 4D workshop report [10]. During the workshop in Krakow, Jamie McClelland from University College London gave an overview of the different imaging modalities (e.g. CT, 4DCT, CBCT, MRI or US), surrogate data, and possible motion modelling approaches that have been proposed, and discussed the advantages and disadvantages of the different options. He underlined the necessity of using suitable imaging data for modelling different types of motion, e.g. models that include breath-to-breath variations in the respiratory motion should not be built from respiratory correlated images (4DCT, 4D-MRI, 4D-CBCT) which are based on the assumption of reproducible breathing [71].

Motion models have a wide range of potential applications. Prior to the treatment they might be useful for probabilistic and robust treatment planning to predict the expected inter- and intra-fractional changes that can occur later during the treatment delivery. They may also be used retrospectively after the treatment to better estimate the delivered dose to improve outcome correlations. Motion models could help inform adaptive treatment strategies, and could also be valuable for online guided treatment delivery. In this context further insights on the optimal choice of the motion surrogate, either from external device, X-ray imaging or US are needed. Furthermore, it is essential to establish the required accuracy for online guidance and to develop methods for ensuring the models are sufficiently accurate. There are many remaining challenges for the clinical use of motion models in particle therapy, but they may ultimately offer superior information for planning, guiding, and assessing treatments than is currently available.

b. Artificial intelligence in 4D particle radiotherapy

The application of artificial intelligence (AI) in oncology has the potential to improve treatment precision at reduced costs and operation time. This has been applied mainly in the field of diagnostic imaging, with an expected increasing role in radiation oncology. In general, AI refers to the information processing by cognitive computer systems, while its subset, machine learning (ML), refers to intelligent computer algorithms able to learn without being explicitly programmed [72]. In healthcare practice, particularly diagnostic imaging, ML offers automated feature extraction (e.g. classification or detection) performed by neural networks and known as deep learning (DL). The AI impact on healthcare is frequently correlated with big data analysis (imaging or clinical data) allowing more accurate treatment outcome and patient prognosis prediction, and therefore treatment decision support [73]. For instance, during the Krakow workshop, a poster by Szmul et al. reporting on AI-based automated lung segmentation for analysis of radiation induced damage has been presented.

Different AI applications in radiation therapy and imaging were discussed in research presentations during the Sapporo and Krakow workshops. The ML applications in 4D particle therapy, as discussed, for instance, by Marcel van Herk from University of Manchester during Krakow workshop, are most often associated with radiological image analysis for anatomy segmentation, but other applications as treatment planning and treatment adaptation, machine and patient quality assurance, as well as treatment delivery and monitoring, are already being explored. The significance of learning from every treated patient in order to develop accurate and efficient methodology of image analysis, mainly to support the process of contouring, was highlighted during the workshop. The wide range of applications of ML methods in imaging and radiation therapy has been summarized in the recent publication by El Naqa et al. [72].

Speakers of both workshops presented and discussed also the role of filtering for transfer learning and diversification (data augmentation) of input data for generating simpler (reduced) or more diverse input data sets.

At the 2018 workshop in Sapporo, Toshiyuki Terunuma from University of Tsukuba presented a talk on a new strategy to personalized deep learning using real-time projected-CTV contouring in X-ray fluoroscopy [74] and preliminary results of the study [75,76]. The key points of the proposed strategy are: 1) to realize patient-specific DL by generating training data from a single patient, 2) to differentiate the importance of image features by the difference in co-occurrence probability caused by the random overlap method, and 3) to track target shape using a deep neural network for segmentation. The learning was achieved employing data augmentation method and feeding SegNet image segmentation algorithms [77] with digitally reconstructed radiographs (DRRs) as the input images, and obtaining the projected CTVs as the output image. A preliminary result using clinical kV X-ray fluoroscopic images of a lung cancer patient showed that the location and shape of projected-CTV could be smoothly traced, even when in fluoroscopic images the tumor overlapped the spine and is less visible [75]. In further, a similar patient-specific strategy was used for pancreas tumor tracking [78]. In this DL method, patient-specific data augmentation was achieved by utilizing a motion vector field (MVF) to deform planning CT images to corresponding 4DCT.

Although presently there are only a few reports on application of DNN (deep neural network) in IGRT (image-guided radiation therapy), there are many aspects that need to be addressed for practical use. Nevertheless, DL-based image processing tools show great potential, which will have an indispensable impact on the future development of IGRT.

c. Future challenges: FLASH and proton arc therapy (PAT)

Recently, an emerging approach to radiation therapy based on the application of ultra-high dose rates of different radiation types to reduce normal tissue toxicity, i.e. the so-called FLASH effect, gained attention. Furthermore, rotational irradiation techniques, as well-known for photons, e.g. VMAT (Volumetric Modulated Arc Therapy), are currently being translated to particle therapy as proton arc therapy (PAT). An overview about the clinical potential of FLASH and proton-arc methods was given in a talk by Anthony Lomax from PSI during the 4D workshop in Krakow.

The main principle of FLASH therapy is to deliver the dose at ultra-high dose rates of tens of Grays per second even in microsecond pulses [79]. First preclinical in vitro and animal studies on FLASH effect demonstrated the feasibility of reducing the toxicity of healthy tissues, while maintaining the same tumor control in comparison to conventional approaches [80–82]. Normal tissues sparing is often associated with the hypothesis that high dose rates lead to oxygen depletion in cells sparing radiation sensitive targets from highly reactive oxygen radicals, while the direct effect of radiation remains the same [79].

The FLASH therapy, if applied clinically, might have a great impact on the radiotherapy of moving targets. The very fast FLASH irradiation, performed in the total time of even less than one second and offering reduced normal tissue toxicity, might modify the need of motion mitigation in treatment of moving targets with photon radiotherapy and particles. However, before reaching the clinical implementation and taking the advantages of FLASH therapy, many challenges have to be addressed. Some of the concerns are related to, e.g. the decision on delivery of single or fractionated treatments with broad or pencil FLASH beams, requirements of treatment planning conformity, treatment plan physical and biological robustness, as well as fundamental understanding of biological and chemical mechanisms standing behind the FLASH effect. Even though FLASH therapy has a large potential in radiotherapy, which has been also presented in case of proton therapy [83], experts from different fields of research need to cooperate to better understand the basis of FLASH effect and to elaborate, and validate optimal protocols for its safe clinical implementation. It is also inseparably linked to the technological challenges, which should be addressed by equipment providers.

ARC therapy relates to the continuous dose delivery during gantry rotation around the patient and is commonly used in radiotherapy using photon beams (VMAT). Recent studies have shown the feasibility of introducing this method also to proton therapy [84], which could result in an improved target conformality and increased robustness in comparison to IMPT plans. However, understanding the clinical impact of PAT on integral dose and OAR exposure requires further studies. Toussaint et al. investigated the impact of increased number of proton beams on physical as well as biologically equivalent doses [85]. Due to the higher low-dose and low-LET volumes authors highlighted that further studies regarding the risk of secondary tumors with PAT technique are required. Although the technique might have a large potential for certain clinical indications, it is not currently available in a clinical setting.

4. Shared efforts of the 4D PBS-PT community

Since the establishment of the 4D treatment planning workshop in 2009, tremendous progress has been made concerning the treatment of moving targets with pencil beam scanned proton therapy (PBS-PT). Concerning this topic, the medical physics field has moved from research driven investigations simulating different 4D treatment approaches to clinically oriented implementation studies, focusing on the safety, practicability and efficiency of 4D treatments. The number of PBS-PT centers treating moving indications is constantly rising and thus, the desire to share experience and establish the best practice is rising.

During the last years several surveys have been conducted to assess the current practice of 4D PBS-PT treatments. In 2013/2014 a survey was conducted by the organizers of the annual 4D treatment planning workshop. Out of the 11 participating centers, 5 were treating moving indications at that time and 4 anticipated to start with 4D treatments in the next 1–2 years. No standardized approach was followed for 4D treatments and as main needed developments smoother adaptive workflows, faster robustness analysing tools and faster delivery options were named. In 2016, the European Particle Therapy Network (EPTN) workgroup 4 on image guided proton therapy (IGPT) conducted a survey assessing practice patterns of image guided particle therapy in Europe specifically addressing the treatment of moving targets [50]. As a result it was reported that most centers developed their own IGPT strategies, being tightly connected to their specific technical implementation and dose delivery methods. This tendency was also reflected in the talks of the Sapporo and Krakow workshops reporting on clinical and medical physics experience in different facilities. Moreover, surveys are also important to inform the community and work towards standardization, e.g. recently, the POP-ART PT survey has been closed, which was aiming to assess patterns of practice for adaptive and real time particle therapy [86].

Besides the participation in surveys and the consideration of their results, active participation in working groups, committees and consortia is beneficial, especially for teams that are in the process of clinically implementing 4D PBS-PT treatment approaches. The EPTN runs working groups on image guidance in particle therapy (Work Package 4) and treatment planning systems (TPS) in particle therapy (Work Package 5) with dedicated sub-groups addressing the treatment of moving targets (https://www.estro.org/Science/EPTN). The Particle Therapy Co-Operative

Group (PTCOG) sustains clinical and technical subcommittees on breast, lymphoma and thoracic PT treatments among others (https://www.ptcog.ch/index.php/other-ptcog-sub-committees). Recently the Real-time adaptive particle therapy of cancer (RAPTOR) consortium was funded (https://raptor-consortium.com/) which invites members of the community to participate in working towards a paradigm shift from manual stepwise to automatic seamless treatment approaches, assuring a standardized implementation of real-time adaptive PT. The consortium is also a part of Marie Skłodowska-Curie Innovative Training Network.

Contributions from working groups, committees and consortia mainly on the following topics are expected in the coming years:

- How can the preliminary clinical PBS-PT treatment approaches for targets of smaller motion amplitude (informally named “small movers”) can be extended to those, whose amplitude is significantly larger (informally named “big movers”)? To answer this advanced 4D robustness evaluation tools will be required and the introduction of simple and straight forward motion mitigation approaches
- How can we validate the accuracy of dose accumulation to assure a consistent and reliable 4D dose reconstruction and monitoring?
- How can we automate steps throughout the 4D PBS-PT workflow (contouring, plan optimization, plan acceptance, patient specific quality assurance, treatment verification among others) to enable real-time 4D adaptive PBS-PT treatments?

4D PBS-PT treatment approaches and tools are complex, thus it will be essential to closely work together as a community, to share experience, learn from each other and establish guidelines and a consensus on the best clinical practice.

5. Conclusions

The annual 4D workshop on particle therapy is a unique opportunity for clinicians and medical physics researchers to share the knowledge about the treatment of moving targets with scanned particle beams. The rapid development of 4D tools, delivery systems and a great amount of research work performed in the 4D field over the last decade enabled entering the phase of actual clinical implementation of 4D particle therapy. As it was shown during the workshops in Sapporo and Krakow, many centers have already started 4D clinical operation applying center-specific, in-house designed 4D protocols. Nevertheless, further developments and standardized guidelines are needed to guarantee consistency between protocols applied at different facilities that may lead to multi-institutional clinical trials needed in both 3D and 4D particle therapy. The cooperation between research groups, clinics, and vendors is indispensable to progress in the 4D therapy development and clinical implementation.

We are proud to announce that the 12th edition of the 4D workshop of particle therapy will be held in 2021 at HollandPTC in Delft, The Netherlands (contact: 4dworkshop.aknopf@gmail.com). The facility started clinical operation in 2018 and is equipped with two pencil beam scanning gantries with integrated CBCT modality, in-room CTs, a beam line dedicated to the treatment of ocular tumors, and a research beam line.

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