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Report of Dedicated Workshops

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Advances in 4D Treatment Planning for Scanned Particle Beam Therapy – Report of Dedicated Workshops

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We report on recent progress in the field of mobile tumor treatment with scanned particle beams, as discussed in the latest editions of the 4D treatment planning workshop. The workshop series started in 2009, with about 20 people from 4 research institutes involved, all actively working on particle therapy delivery and development. The first workshop resulted in a summary of recommendations for the treatment of mobile targets, along with a list of requirements to apply these guidelines clinically. The increased interest in the treatment of mobile tumors led to a continuously growing number of attendees: the 2012 edition counted more than 60 participants from 20 institutions and commercial vendors. The focus of research discussions among workshop participants progressively moved from 4D treatment planning to complete 4D treatments, aiming at effective and safe treatment delivery. Current research perspectives on 4D treatments include all critical aspects of time resolved delivery, such as in-room imaging, motion detection, beam application, and quality assurance techniques. This was motivated by the start of first clinical treatments of hepato cellular tumors with a scanned particle beam, relying on gating or abdominal compression for motion mitigation. Up to date research activities emphasize significant efforts in investigating advanced motion mitigation techniques, with a specific interest in the development of dedicated tools for experimental validation. Potential improvements will be made possible in the near future through 4D optimized treatment plans that require upgrades of the currently established therapy control systems for time resolved delivery. But since also these novel optimization techniques rely on the validity of the 4DCT, research focusing on alternative 4D imaging technique, such as MRI based 4DCT generation will continue.

Key words: Particle therapy; Proton therapy; Beam scanning; Organ motion; Interplay; 4D.

Introduction

In this report of the 4th 4D treatment planning workshop held in Erlangen, Germany in December 2012 we want to review the recent progress that has been made in the field of mobile tumor treatment with scanned particle beams with an emphasis on the contributions discussed within the workshop.

Abbreviations: 3D: Three Dimensional; 4D: Four Dimensional, Time Resolved; 4DCT(MRI): MRI Motion Trace Based 4DCT Generation; CN: Conformity Number; CNAO: Centro Nazionale di Adroterapia Oncologica; CT: Computed Tomography; CTV: Clinical Target Volume; DKFZ: German Cancer Research Center, Heidelberg, Germany; DVH: Dose Volume Histogram; GSI: GSI Helmholtzzentrum für Schwerionenforschung, Darmstadt, Germany; HIT: Heidelberg Ion Beam Therapy Center, Heidelberg, Germany; ICRU: International Commission on Radiation Units & Measurements; IMPT: Intensity Modulated Particle Therapy; ITV: Internal Target Volume; MRI: Magnetic Resonance Imaging; NIRS: National Institute for Radiological Sciences, Chiba, Japan; PCA: Principle Component Analysis; PCR: Phase-controlled Rescanning; PET: Positron Emission Tomography; PSI: Paul Scherrer Institute, Villingen, Switzerland; SIFT: Scale Invariant Feature Transform; SGSMP: Swiss Society of Radiobiology and Medical Physics.

The workshop series started in 2009 at the Paul Scherrer Institute (PSI), Villigen, Switzerland. About 20 people attended from 4 institutes (GSI Helmholtz Centre for Heavy Ion Research (GSI), Darmstadt, Germany, German Cancer Research Center (DKFZ), Heidelberg, Germany, University of Tübingen, Tübingen, Germany, PSI). A special report was published as a result of the discussions in the plenary sessions of the workshop (1). It summarizes recommendations for the treatment of mobile targets with actively scanned particles and contained a list of requirements to elaborate and apply these guidelines. The paper was awarded with the Swiss Society of Radiobiology and Medical Physics (SGSMP)/ Varian recognition award 2010. In 2010, the 2nd edition of the workshop was carried out at GSI with about 30 participants; the 3rd edition 2011 at the CNAO facility, Pavia, Italy already attracted more than 40 participants. To restore the original aim of the workshop, *i.e.*, an informal platform to discuss current approaches, challenges and future research directions in 4D treatment planning, the participants agreed at the 4th edition of the workshop in 2012 at the University of Erlangen-Nuremberg, Germany (about 60 participants from about 20 institution including representative of commercial vendors), that in the future, the number of participants per institute will be limited to two persons. To stimulate discussions on still confidential research projects and to enable an open controversy about failures, representatives of commercial vendors will be excluded. In return, an annual report will be established to summarize all novelty. The next edition of the workshop is planned in November 2013 at PSI, Switzerland.

In the last years, the research on beam scanning for treatment of mobile tumors has finally led to first clinical applications, *e.g.*, for hepato cellular tumors that are subject to respiratory motion (2). These clinical approaches can still be considered as first steps, *i.e.* research work has to continue, mainly in the fields outlined already in the previous report of Knopf *et al.* In that context, the scope changed from 4D treatment planning to complete 4D treatments, including appropriate imaging, motion detection, beam application, and quality assurance techniques suitable for the interplay prone irradiation of mobile tumors with a scanned beam.

The structure of the report is geared to the outlook chapter of the report summarizing the 1st workshop (1). We will focus on progress in 4D treatment planning options and in 4D treatment application techniques with an emphasis on contributions from participants of the workshop. For a broader overview on the field of the treatment of mobile tumors with scanned particle beam therapy please consult one of the following recent review papers (3-5). Even broader knowledge on cross-cutting aspects such as motion monitoring for treatment of mobile tumors exists in the photon treatment community; for details we refer the reader to review articles (6-8).

Progress in 4D Treatment Planning

4D Dose Calculation

4D dose calculation is an essential part of 4D treatment and has been first reported for proton therapy almost a decade ago (9). Also for scanned particle beams research codes capable of 4D dose calculations have been established at several centers in the last years (10-14), providing the foundation for more advanced research as mentioned below. The codes include handling of proton as well as particle beams and apart from analytical codes also Monte Carlo based solutions have been reported (15-17). The advanced codes enable 4D dose calculations taking into account different delivery parameters as well as numerous realistic patient motion scenarios (11, 18). Thus, simulation of different application techniques (*e.g.*, active vs. passive energy modulation, rescanning vs. beam tracking) as well as the patient specific reconstruction of treatment deliveries is possible (see section 5.4).

4D dose calculation is not limited to intra-fractionally moving tumors but also inter-fractionally changing geometries such as prostate cancer was studied and presented at the workshops. The motion phases are then from multiple days and, *e.g.*, represent different rectum filling. Another intermediate approach between 3D and full 4D treatment planning is the dose calculation on repeated breath hold CTs. The robustness of proton treatment plans for lung cancer patients against interfractional variations during voluntary breath hold was recently studied in a master project carried out at PSI (19).

Based on the activity of the last years, codes for 4D dose calculation are no longer the bottleneck for precise studies assessing the dosimetric outcome of treatment techniques or even delivered treatments. The challenge in the next years will be the transition from research codes into a commercially available product and the development of robust deformable image registration codes since vector field are an essential input to 4D dose reconstruction algorithms.

Motion Modeling for 4D Planning

As in 3D treatments, many of the 4D treatment planning approaches currently rely on the 4DCT acquired during treatment planning. This dataset represents a snapshot of the patient's motion and many studies showed that the motion parameters change during the course of treatment and even within a few minutes (20-22). It is thus essential to exactly quantify the expected changes and their dosimetric influence and to develop solutions that overcome that clinical situation. In addition, the community needs to strive for better image guidance options which are still less advanced in particle therapy centers than in the photon treatment community despite the fact that particle treatments can physically

be delivered more precisely. Then, *e.g.*, 4D Cone-Beam CTs could be acquired of an immobilized patient and ideally be used in an online, adaptive treatment option (23).

The issue of accurate motion modeling in 4D treatment planning has been addressed by investigating the effects of breathing irregularities in 4DCT (24). Higher correlation between external surrogates and internal lung motion was found for regular vs. irregular breathers, with prediction errors mostly dependent on the peak to peak range of motion. A novel 4D CT resorting technique based on the use of multiple surrogates has been also investigated: results show that monitoring of multiple surrogates can handle the task of breathing phase detection more accurately, resulting in reduced image artifacts in presence of limited breathing irregularities (25).

To overcome the restriction of snap shot 4DCTs and to reduce imaging dose, PSI investigated, if 4D magnetic resonance imaging (MRI) data can be the basis for 4DCT generation, named 4DCT(MRI) (12). 4DMRI can be acquired over several minutes since no ionizing radiation is applied. Boye *et al.* extracted motion vectors from the 4DMRI and wrapped them to stationary 3DCT to derive 4DCT(MRI)s with the help of motion modeling. 4DCT(MRI)s obtained in this way represent motion behavior over several breathing cycles including variations in amplitude and breathing frequency as well as baseline drifts. Thus, no assumptions on breathing regularity have to be made during 4D treatment planning. This enables the investigation of treatment plans against motion variations. Furthermore, motion variations can be considered in treatment plan optimization in order to obtain 4D optimized plans that are robust against expected variation such as phase shifts between motion surrogate and the actual tumor motion. 4DCT(MRI)s can further be used to support motion monitoring, as described in section 5.1.

Evaluation of Different Deformable Registration Methods

4D treatment planning heavily relies on deformable image registration. Numerous codes are available from vendors and within the research community. Since the application of those codes varies, also the research on their validation does. In a cross-center study, Brock *et al.* studied various codes for typical radiotherapy sites with respect to accuracy and reproducibility (26). They report large discrepancies in the reported shifts with a majority of the codes performing at voxel size level of the underlying dataset.

Among the workshop participants, an automatic feature detection was proposed relying on the Scale Invariant Feature Transform (SIFT) method for validation of deformable image registration (27). The automated detection results are comparable to expert-user-based detection, and is applicable to both 4D CT and 4DMRI datasets (28). The method was studied in adaptive radiotherapy and showed that SIFT based metrics are correlated to detected anatomical changes over the course of treatment. Also the use of regularization methods in deformable image registration was analyzed, as a way to increase the physiological consistency of the quantified deformation field (29). This has been applied to head & neck treatments and requires extension to mobile sites, in order to establish optimal regularization parameters.

A detailed study with respect to 4D dose calculation in scanned proton beams has been reported by Zhang *et al.* (18). For single-field treatments, where no motion mitigation was used a maximum (mean) dose difference (averaged over three cases) of 32.8% (2.9%) was observed with regards to the use of different deformable registration algorithms to extract motion information from 4D images. This registration ambiguity-induced uncertainty indicate the necessity to interpret 4D dose distributions for scanned proton therapy as approximation, inevitably bonded with error bars. Quantification and presentation of deviations in 4D treatments is an essential topic in itself. Not only the registration quality but also many of the other parameters such as internal-external correlation of motion monitoring devices or assumptions in the treatment application technique are prone to uncertainties. Hild *et al.* proposed different quantification options on the basis of 4D treatment plans for lung tumors (30).

Lüchtenborg used different registration options in a treatment planning study assessing beam tracking (31). They report, that rigid registrations should be used for calculation of beam tracking parameters since distances are preserved which is essential if over/under-doses due to changes in spacing of Bragg-peaks should be avoided.

4D Treatment Plan Optimization

4D treatment plan optimization can be classified as the explicit incorporation of motion data into the cost function of the optimization. It has been reported especially in the photon community since several years (32) also within the context of our workshop series, which included the studies of Suh *et al.* (33, 34).

The potential of 4D optimized treatment plans are one of the results of a recent study of Knopf *et al.* (35). They studied the consequences of different beam weight distributions when treating mobile targets. For static targets, beam weights were optimized in order to achieve best target dose conformity. This usually results in many low weighted spots and a few high weighted spots at the distal edge of the target. For the treatment of mobile tumors target dose conformity is compromised by blurring, thus different beam weight optimization objectives might be considered. In their preliminary study it was shown that treatment plans with a "smooth"

beam weight distributions are significantly more robust when treating moving targets with scanned proton beams (36). By designing appropriate robustness constraints, such smooth distribution could be the outcome of a treatment plan optimized in 4D.

Eley *et al.* investigated the possibilities of 4D optimization in beam tracking with a scanned carbon beam (37). They investigated for an artificial geometry as well as for a lung tumor patient, if 4D optimized treatment plans could reduce the dose to nearby organs at risk. The GSI in-house treatment planning system was thus extended to fully incorporate 4DCTs and deformation maps in the optimization process. They found comparable target coverage for both cases and a reduced maximal dose to the heart as organ at risk.

The work is complemented by Graeff *et al.*, who developed a more general framework for 4D optimization based on subdividing the target volume to ease the technical demands in the optimization. This is promising or even essential, since memory and calculation time demands might be too high, if all (typically $\sim$10) motion states are incorporated without further constraints. The sub-sections of the target volume are chosen with respect to the delivery constraints. The authors showed for nine lung cancer patients that highly conformal target dose distributions can be achieved without detrimental inverse interplay patterns in the entrance channel which are typically observed in beam tracking plans (38). An alternative approach is reported by Graeff *et al.* in this issue.

As in 4D dose calculation, also 4D optimization still relies on precise 4DCT and deformation vector field data. Appropriate procedures and/or techniques have to be established and assessed prior clinical use (see also section 4.2).

Strategies for 4D Treatment Planning Studies

Due to interplay effects, the dose homogeneity throughout the target is the main concern in the treatment of mobile targets with scanned particle therapy. Different homogeneity benchmarks are reported. It was proposed to unify the reporting of DVH parameters to make studies more comparable. The proposed, already well-established parameters include: D5-D95 for the homogeneity of the target dose, V95 to quantify target coverage, and V107 for overdose. For dose conformation, the conformity number (CN) as described by van't Riet (39) is proposed.

It should be noted, that quantification of treatment techniques for moving tumors with a scanned beam should be based on multiple simulations or measurements using different parameters for both target motion and beam application. Due to interplay, all techniques will be influenced by the specific interference pattern of an individual irradiation (40) and thus a single outcome is not representative for the potential of a technique.

Experimental Validation of 4D Treatments

Experimental validation of implemented 4D treatment options is essential since the technical demands of the treatment delivery systems are often much higher than for 3D treatments and can thus be the bottleneck of potential solutions. Validation requires adequate motion phantoms with detections systems. A list of phantom features was reported in the previous workshop report (1).

Each group performing experiments focusing on moving targets uses motion platforms, either commercial solutions or in-house built. These devices allow typically a one-dimensional (translational or rotational) motion which is not representing a patient geometry but often sufficient for an initial study of a new technique. It is then the preferred technique due to easy handling but investigators have to keep in mind that study results might not be transferable to patient geometries. The platforms can carry radiographic films (40), scintillation detectors (41), biological probes (42), probes for positron emission tomography (PET) measurements (43), or water phantoms with ionization chambers (44).

Recently, developments focused on complex phantoms that should mimic the patient geometry. Zakova *et al.* together with the Centre Suisse d'Electronique et de Microtechnique (CSEM) currently develop an anthropomorphic thorax phantom which is completely metal-free and CT as well as MRI compatible (45). Motion can be controlled by air inflation into an air-tight lung, which is surrounded by a realisticly expanding rib cage. The dose distribution can be recorded with an ionization chamber or Gafchromic films placed directly into a tumor moving within the lung compartment. First irradiation tests with a scanned proton beam showed that the phantom allows extensive dosimetric studies under realistic circumstances (45). Steidl *et al.* report about a robot based thorax phantom which is used for validation studies in scanned carbon beams (46). A robotic arm is used to move a lucite block mimicking the tumor and equipped with radiographic films and 20 ionizations chambers. The tumor can move in 6D and motion is in correlation with an independent thorax phantom that is based on a plastic skeleton covered by rubber representing the skin. Initial tests with and without beam have been successful (46) and the phantom has since been used in a number of 4D validation studies (11, 47).

On the experimental side, the feasibility and efficacy of the advanced scanning techniques was tested systematically in numerous studies. Rescanning (41), gating (48), beam tracking (44, 49) as the main motion mitigation techniques, but also the validity of 4D treatment planning systems (11, 38, 50)

have been studied. More details will be reported in section 5 covering the mitigation techniques itself.

Validation further includes *in vivo* dosimetry. An established method for ion beam therapy is the in-beam and offline use of PET. Carbon-11 and C-10 that result of fragmentation of the primary C-12 beam serve as positron emitters (51). In the last years the Helmholtz-Centre Dresden Rossendorf (HZDR), GSI and HIT worked on 4D extensions for in-beam PET within the EU funded projects ULICE and ENVISION. Laube *et al.* reported on simulations, reconstruction methods and experimental results for 4D in-beam PET (43, 52). The proposed methods are suitable to judge the relevant parameters for treatments of intra-fractionally moving tumors with a scanned carbon beam. Initial steps towards routine implementation at the HIT facility have been successful (17).

Activities based on 4D PET further focused on the use of 4D CT motion models to optimize 4D PET imaging (53, 54). Such an optimization can either be applied to treatment planning 4D PET/CT studies or to post-irradiation PET imaging (PET-based dosimetry), in order to make the most of the reduced count statistics induced by particle irradiation.

Despite all efforts, validations will always lack the clinical scenario and typically focus on one special technique (*e.g.*, motion phantoms to validate motion monitoring systems that do not allow dosimetric quantification or assessment of deformable image registration). Thus, careful introduction of new techniques into clinical application has to follow despite potential shortcomings accompanied by, *e.g.*, the proposed *in vivo* dosimetry techniques and stringent follow-up of the patients.

Progress in Beam Application Techniques

Treatment of intra-fractionally moving organs will require dedicated means if scanned beams are chosen as treatment technique. In the context of this manuscript we will refer to all procedures as techniques and report the current status of the involved groups. Many of them require precise motion monitoring and often also margins forming the internal target volume (ITV) from the clinical target volume (CTV).

Motion Monitoring and Motion Prediction

Volumetric methods such as 4DCT or 4DMRI are used as part of motion modeling in treatment planning to describe the anatomy for dose calculation and treatment plan optimization. During treatment delivery these methods are not (yet) available, despite first approaches to combine photon linacs and MRI exactly for this purpose (55). Thus, 1D motion signals or motion surrogates are frequently used for the purpose of detecting the 4DCT state or the 3D position of a marker in real-time during treatment delivery (3, 56). Especially for precise treatment techniques like beam tracking (section 5.5), surrogates are not ideal due to potential miscorrelation to the internal targets. Vice versa, purely fluoroscopic based detection of radio-opaque fiducials offers precise motion information, but results in additional x-ray doses (57) even though these can be at dose levels comparable to other image guidance options (58). Thus, alternative techniques have been studied.

In order to precisely track tumor motion online it is essential to obtain information on the 3D motion vector throughout the region of interest. Any sparsely acquired surrogate motion is generally not sufficient to describe the deformable behavior in three dimensions. In a recent study, it has been shown that 3D deformable motions can be estimated from surrogate motions obtained from either BEV or dual X-ray imaging systems for treatments in the liver (59, 60). The method requires motion sampled over a number of breathing cycles for each patient before treatment using some form of 4D imaging, for example 4DMRI. On the base of this motion library a Principle Component Analysis (PCA) can be applied to build subject specific motion models. Motion models based on markerless surface detection have also been explored, relying of deformable surface registration to achieve accurate motion monitoring of specific anatomical landmarks (61).

3D real-time data without ionizing radiation can be measured by ultrasound as shown by several groups for inter-fractional motion assessment (organ positioning) (56). For intra-fractional motion monitoring, Jenne *et al.* reported the use of ultrasound at the 4th workshop in Erlangen. By means of dedicated transducers a 2D plane of the patient can be scanned. Either the tumor is visualized directly, or internal surrogates such as the diaphragm are used. If combined in two directions, pseudo-3D data are achieved. The feasibility of ultrasound based beam tracking has been reported by Prall *et al.* (62). They showed that delay compensation is possible via neural networks and present experimental data indicating the feasibility of ultrasound based compensation without tracking parameters from treatment planning.

At DKFZ motion monitoring using the Calypso-System (Medical Systems Inc., Palo Alto, CA) for internal prostate motion and more recently also for lung tumor motion was studied (63). The system uses field generating coils to be implanted inside or close to the tumor whose position is detected by an electromagnetic detector array. Thus no additional radiation dose is applied to the patient and real time tumor motion tracking is feasible (64, 65). Recent attempts are trying to use the system also for proton therapy (66). In case of tumor tracking accurate and real-time tumor motion detection is required. To overcome the problem of system latencies additional emphasis has been put on the evaluation

of motion prediction algorithms for real-time tumor tracking. The study of Krauss *et al.* emphasized the relative importance of adequate model parameter optimization compared to the actual prediction model selection (67).

A combination of internal motion detection and surrogates can be achieved by dedicated correlation models. The group at Politechnico Milano studied several options, focusing on the accuracy of different correlation models by retrospective clinical data analysis (68-70). The issue of adaptive modeling and robustness of the correlation function of controlled breathing irregularities has been quantified (69, 70). To show feasibility within the scanned particle therapy framework, model based motion detection has been used for beam tracking at GSI (47) (see also section 5.5 and Fattori *et al.* in this issue).

An alternative technique could be particle radiography which has been proposed for different purposes for decades (71, 72). With current technology, radiography as well as tomography is possible (73, 74), but so far not used for intra-fractional target motion detection. Preliminary work has been carried out to study the potential of particle radiography to monitor soft tissue motion (75, 76). In these studies, prior knowledge represented by the treatment planning CT is used to enhance the soft tissue contrast, so that particle radiography can be optimized for motion detection in soft tissue targets, avoiding the use of implanted surrogates to reach adequate accuracy.

Margin-based Approach

Intra-fractional motion is typically dealt with by using margins surrounding the CTV. ICRU report 62 (77) advises that variations in size, shape and position of CTVs relative to anatomic reference points can be considered for ITVs. In addition to geometrical margin adaption, changes of water equivalent path length have to be considered for particle therapy, as already mentioned in the proton report of the ICRU (78). These considerations are applied since several years in passively shaped particle therapy but are often based on, *e.g.*, overwriting of CT-numbers in the planning CT (79).

A number of years ago, Engelsman *et al.* (80) proposed to use 4DCT as basis of ITV definition in scattered proton beam therapy. The work has been implemented for scanned beams as well (81, 82) but the original implementation is limited to single-field uniformal dose approaches because of field-specific mapping of motion induced changes in particle range and uses out-dated dose calculation models. A full consideration that is also applicable to intensity modulated particle therapy (IMPT) has been reported by Graeff *et al.* (83). They transform the geometrical ITV into a field-specific water-equivalent path length ITV and use several motion phases to model the motion depended shape of the range-adapted ITV. The proposed method has been tested successfully on the data of a lung cancer patient.

A recent study by Knopf at al. shows that CTVs significantly differ in size from geometrical ITVs and range adapted ITVs (35). Furthermore, range adapted ITVs and geometrical ITVs differ significantly in size and are spatially displaced, particularly for lung patients. Range-adapted ITVs show a strong field dependency in shape.

Rescanning

One way to overcome interplay effects are multiple irradiations per treatment fraction, referred to as rescanning (84). For acceptable treatment times this approach requires high scan speeds and thus also fast beam monitoring systems. In case of treatment plan application times within minutes, also (multiple) breath-hold based approaches are then feasible. There exist many possible rescanning strategies and naming schemes (scaled/slice-by-slice/level vs. iso-layered vs. volumetric/uniform, (85, 86)). In simulations by Zenklusen *et al.* (86) it was shown that continuous line scanning seems to be the most elegant solution: it provides higher repainting rates and produces superior results but is probably more difficult to realize. Recently the effectiveness of volumetric and slice-by-slice rescanning was investigated in relation to slow and fast beam delivery systems by Bernatowicz *et al.* (87). Similar effect to rescanning can be achieved with multiple fields per plan (10) or by using dedicated fractionation schemes (88).

Rescanning is a strong approach to mitigate interplay effects, but it does not address dose blurring due to motion. Therefore, it is believed that best results can be obtained by combining rescanning with other motion mitigation techniques and/or margins. At NIRS, most likely rescanning will be combined with gating and referred to as phase-controlled rescanning (PCR) (89). They reported several technical and simulation studies in the last years and are close to treat the first patient. Also at PSI rescanning alone is only seen as first level of motion mitigation. As a next step it is foreseen to use gated rescanning or slow tracking (35, 60). The second refers to a treatment during repeated breath holds with an adaption of the beam position for possible variation between different breath holds. As ultimate solutions 4D optimized rescanning or beam tracking and retracking (90) is envisioned.

Gating

Gating has been the method of choice for lung and liver treatments with a scattered carbon beam at NIRS for >10 years (91). Based on motion monitoring data (section 5.1), the beam is only turned on in a defined part of the breathing cycle, typically at end-exhale. Thus, the effective motion

amplitude is reduced. Also for scanned beam delivery this approach will reduce the interplay effects, but gating alone will not result in homogeneous CTV coverage since also reduced amplitudes induce interplay effect. NIRS thus combines gating with rescanning (PCR, see previous section). An alternative seems to be irradiation with increased beam overlap, *e.g.*, larger beam spot sizes at identical raster grid spacing as for stationary tumors (48). Based on numerous simulations and experimental studies of GSI and HIT (92, 93) that included assessment of the sensor delays (94) and dosimetric verification (95), gating was recently introduced clinically for the treatment of hepato cellular cancer at HIT (2). Apart from gating, mainly abdominal compression was used to control the motion extent of the patient, but the required mitigation approaches are similar since in each case the interference effect of residual motion amplitudes needs to be compensated. Richter *et al.* recorded the motion surrogate trace and the scanner progress data during treatment delivery of each fraction and used the GSI in-house 4D treatment planning system to reconstruct the delivered 4D dose distribution for each fraction and for the complete treatment. Even though the focus of that study was feasibility of the proposed method, they could show appropriate CTV coverage for a number of patients (96).

Beam Tracking

Beam tracking uses data from motion monitoring and potentially 4D treatment planning to compensate target motion by adaptation of the scanned pencil beam (49, 97). Previous studies concentrated on simple phantom geometries and had the goal of feasibility checks since the application and therapy control needs are challenging. With respect to system performance (98) but also dosimetrically (49, 99, 100), beam tracking works precisely. In case of non-translational motion, *e.g.*, rotations, adjustment of the pencil beam position is insufficient since the pre-irradiation mainly of proximal parts of the target by distal iso-energy layers changes. Luchtenborg *et al.* studied this influence and proposed an adaption of deposited particle numbers combined with real-time calculations as solution (44).

In 2012, experiments were conducted and reported at the 4th 4D treatment planning workshop that extended from simple phantoms to complex, patient-like geometry. Scenarios based on the robotic thorax phantom presented in section 4.6 were studied using correlation model based motion monitoring solutions from the Politecnico Milano group (see section 5.1). The experiments included baseline drifts of the tumor and correlation mismatch between thorax surface and tumor which will cause dose deviations if beam tracking delivery is fully based on the optimized 4D treatment plan. Thus, in the lateral plane, compensation offsets were directly determined in the motion monitoring system which can therefore compensate changes with respect to the treatment planning 4DCT scan such as baseline drifts. Integration of the system (see Fattori *et al.*, this issue), motion correlation models (47), and also the dosimetric outcome worked as expected. Beam tracking is thus on the verge to commercial implementation or research based clinical assessment.

Delivery of 4D Optimized Treatment Plans

4D optimization incorporates the different phases of the 4DCT data in treatment plan optimization. Apart from dedicated ITV concepts, these algorithms can also result in a 4D treatment plan, *i.e.* parameter files that are dependent on the motion phase of the patient. Such plans require a dedicated treatment control system which is more complex than for 3D treatments and of similar but different complexity to particle number compensated beam tracking. Such a control system has been implemented at GSI and its feasibility has been shown for different flavors of 4D optimization.

For both 4D optimization methods described above, the treatment plan consists of a set of 3D plans to be delivered to specific motion phases. The treatment control system thus switches between these plans according to a motion monitoring signal. Depending on target geometry and the irradiation sequence determined by the target motion, some motion phases do not or no longer require irradiation. In this case, the beam is gated during this motion phase. Smooth delivery thus requires fast, multiple gating during a spill. Delivery can be greatly facilitated by intensity control and flexible spill timing.

It should be noted that for these methods, the sequence of beam spots is determined online by the actual measured motion. A specific scanpath as for 3D delivery can thus not be preplanned. For both methods, the feasibility of delivery was shown in a film experiment (38).

Concluding Remarks

Scanned particle beam application to intra-fractionally moving tumors are still challenging, but the developments reported within the scope of the four 4D treatment planning workshops and on other occasions show that methods and techniques have been developed that will allow safe treatment deliveries at several centers with a strong research focus in the near future. First patients have already been treated at HIT with a scanned carbon beam and gating or abdominal compression as motion mitigation technique and at Rinnecker Proton Therapy Center in Munich, Germany using apnea. PSI will rely on rescanning and potentially gating, NIRS plans to mimic scattered beam applications by rescanning used in combination with beam gating as in the current clinical practice.

The achievements reported above are predominantly reported by and implemented in centers with a strong research focus. One of the main challenges will be the transition of those ideas into medical products that vendors can offer to all facilities of the meanwhile fairly broad particle therapy community using beam scanning. While many of the new machines, *e.g.*, can provide fast beam gating, there is typically no 4D treatment planning functionality available that would support parameter choices based on assessment of the expected 4D dose distribution. One potential reason for that slow transition into products could be the zoo of options reported from the research community with no clear component portfolio visible yet. For each of the required technologies (motion monitoring, motion mitigation, treatment planning, …) there are several options available, some of them even in clinical use, such as correlation model based motion monitoring, as in the Cyberknife Synchrony or the Brainlab/Mitsubishi Vero system, but the required or at least beneficial integration into a particle therapy center is not yet available. Many of those options were developed for photon radiotherapy, another indication that the particle therapy community still applies other standards than the modern photon therapy techniques. Similar for 4D verification systems and a quality assurance workflow, which was not covered in sufficient detail in this workshop series but which will require new ideas due to the random and thus not really predictable manner of interplay effects. That integration might speed up in case of standardization, *i.e.* defined protocols for, *e.g.*, the beam delivery sequence or the motion monitoring signal such that different 4D treatment planning systems could import the data for calculation of the delivered 4D dose distribution.

From a research perspective there is still the need for precise and three dimensional motion monitoring, ideally including the range of the particle beam. Potential solutions, such as 4DCT(MRI) in combination with a surrogate and a PCA based model have been proposed recently (12, 60) and also 4DPET or prompt-γ imaging might allow real-time options at some point. Ideally, such precise imaging options have to be combined with (real-time) treatment plan adaptation algorithms to allow precise treatments of moving organs even in hypofractionated or even single-fraction treatment schedules (stereotactic body particle radiosurgery). The management of variable uncertainties including interplay effects in fewer fractions becomes even more challenging since the fractionation itself will not lead to mitigation of dose inhomogeneities (10, 101, 102). Still, such fractionation schemes proved to be effective in clinical studies at NIRS (103) and thus wide-spread use can be anticipated not only because they are preferred by many patients.

For the still pretty young workshop series and future generation of researchers these challenges are motivating and the clinical results of the first patients treated with the advanced mitigation techniques mentioned within the scope of this report will certainly trigger new ideas. The next option to exchange experiences and details within that field will be the 5th workshop, taking place at PSI in Villigen, Switzerland on November 28/29 2013. Interested colleagues – especially radio-oncologists – can contact one of the authors.

References

1. Knopf A, Bert C, Heath E, Nill S, Kraus K, Richter D, Hug E, Pedroni E, Safai S, Albertini F, Zenklusen S, Boye D, Sohn M, Soukup M, Sobotta B & Lomax A. Special report: workshop on 4D treatment planning in actively scanned particle therapy–recommendations, technical challenges, and future research directions. *Medical Physics 37*, 4608-4614 (2010). PMID: 20964178
2. Habermehl D, Debus J, Ganten T, Ganten MK, Bauer J, Brecht IC, Brons S, Haberer T, Haertig M, Jaekel O, Parodi K, Welzel T & Combs SE. Hypofractionated carbon ion therapy delivered with scanned ion beams for patients with hepatocellular carcinoma – feasibility and clinical response. *Radiation Oncology 8*, 59 (2013). PMID: 23497349
3. Bert C & Durante M. Motion in radiotherapy: particle therapy. *Physics in Medicine and Biology 56*, R113-R114 (2011). DOI: 10.1088/0031-9155/56/16/r01
4. Mori S, Zenklusen S & Knopf AC. Current status and future prospects of multi-dimensional image-guided particle therapy. *Radiol Phys Technol 6*(2), 249-72 (2013). PMID: 23420206
5. Riboldi M, Orecchia R & Baroni G. Real-time tumour tracking in particle therapy: technological developments and future perspectives. *Lancet Oncology 13*, E383-E391 (2012). DOI: 10.1016/S1470-2045(12)70243-7
6. Korreman SS. Motion in radiotherapy: photon therapy. *Physics in Medicine and Biology 57*, R161-R191 (2012). DOI: 10.1088/0031-9155/57/23/r161
7. Hugo GD & Rosu M. Advances in 4D radiation therapy for managing respiration: part I – 4D imaging. *Zeitschrift fur medizinische Physik 22*, 258-271 (2012). DOI: 10.1016/j.zemedi.2012.06.009
8. Rosu M & Hugo GD. Advances in 4D radiation therapy for managing respiration: part II – 4D treatment planning. *Zeitschrift fur medizinische Physik 22*, 272-280 (2012). DOI: 10.1016/j.zemedi.2012.06.011
9. Rietzel E, Chen GTY, Choi NC & Willet CG. Four-dimensional image-based treatment planning: Target volume segmentation and dose calculation in the presence of respiratory motion. *International Journal of Radiation Oncology*Biology*Physics 61*, 1535-1550 (2005). PMID: 15817360
10. Knopf AC, Hong TS & Lomax A. Scanned proton radiotherapy for mobile targets-the effectiveness of re-scanning in the context of different treatment planning approaches and for different motion characteristics. *Physics in Medicine and Biology 56*, 7257-7271 (2011). DOI: 10.1088/0031-9155/56/22/016
11. Richter D, Schwarzkopf A, Trautmann J, Kraemer M, Durante M, Jaekel O & Bert C. Upgrade and benchmarking of a 4D treatment planning system for scanned ion beam therapy. *Medical Physics 40* (2013). DOI: 10.1118/1.4800802
12. Boye D, Lomax T & Knopf A. Mapping motion from 4D-MRI to 3D-CT for use in 4D dose calculations: A technical feasibility study. *Medical Physics 40* (2013). DOI: 10.1118/1.4801914
13. Kraus KM, Heath E & Oelfke U. Dosimetric consequences of tumour motion due to respiration for a scanned proton beam. *Physics in Medicine and Biology 56*, 6563-6581 (2011). DOI: 10.1088/0031-9155/56/20/003
14. Poulsen P, Worm ES, Hoyer M, Grau C & Petersen JB. in *PTCOG 53* (Essen, 2013).

15. Paganetti H, Jiang H & Trofimov A. 4D Monte Carlo simulation of proton beam scanning: modelling of variations in time and space to study the interplay between scanning pattern and time-dependent patient geometry. *Physics in Medicine and Biology 50*, 983-990 (2005). PMID: 15798270
16. Dowdell S, Grassberger C, Sharp GC & Paganetti H. Interplay effects in proton scanning for lung: a 4D Monte Carlo study assessing the impact of tumor and beam delivery parameters. *Physics in Medicine and Biology 58*, 4137-4156 (2013). DOI: 10.1088/0031-9155/58/12/4137
17. Kurz C, Bauer J, Bert C, Bongers A, Jenne J, Richter D, Saito N, Schoenahl F, Unholtz D & Parodi K. First steps towards 4D offline PET-based treatment verification at the Heidelberg ion beam therapy center. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology 102*, S55-S56 (2012).
18. Zhang Y, Boye D, Tanner C, Lomax AJ & Knopf A. Respiratory liver motion estimation and its effect on scanned proton beam therapy. *Physics in Medicine and Biology 57*, 1779-1795 (2012). DOI: 10.1088/0031-9155/57/7/1779
19. Dueck J. Robustness of the voluntary breath-hold approach for the treatment of early stage lung cancer with spot scanned proton therapy M.Sc. thesis, Lund University (2013).
20. Sonke JJ, Lebesque J & van HM. Variability of four-dimensional computed tomography patient models. *International Journal of Radiation Oncology, Biology, Physics 70*, 590-598 (2008). PMID: 18037579
21. Britton KR, Starkschall G, Tucker SL, Pan T, Nelson C, Chang JY, Cox JD, Mohan R & Komaki R. Assessment of gross tumor volume regression and motion changes during radiotherapy for non-small-cell lung cancer as measured by four-dimensional computed tomography. *International Journal of Radiation Oncology, Biology, Physics 68*, 1036-1046 (2007). PMID: 17379442
22. Seppenwoolde Y, Shirato H, Kitamura K, Shimizu S, Lebesque JV & Miyasaka K. Precise and real-time measurement of 3D tumor motion in lung due to breathing and heartbeat, measured during radiotherapy. *International Journal of Radiation Oncology*Biology*Physics 53*, 822-834 (2002). PMID: 12095547
23. Sonke JJ, Zijp L, Remeijer P & van Herk M. Respiratory correlated cone beam CT. *Medical Physics 32*, 1176-1186 (2005). PMID: 15895601
24. Spadea MF, Peroni M, Preve E, Riboldi M, Baroni G, Chen GTY & Sharp GC. Uncertainties in lung motion prediction relying on external surrogate: a 4DCT study in regular vs. irregular breathers. *Technology in Cancer Research & Treatment 9*, 307-315 (2010). PMID: 20441241
25. Gianoli C, Riboldi M, Spadea MF, Travaini LL, Ferrari M, Mei R, Orecchia R & Baroni G. A multiple points method for 4D CT image sorting. *Medical Physics 38*, 656-667 (2011). DOI: 10.1118/1.3538921
26. Brock KK. Results of a multi-institution deformable registration accuracy study (MIDRAS). *International Journal of Radiation Oncology, Biology, Physics 76*, 583-596 (2010). DOI: 10.1016/j.ijrobp.2009.06.031
27. Paganelli C, Peroni M, Riboldi M, Sharp GC, Ciardo D, Alterio D, Orecchia R & Baroni G. Scale invariant feature transform in adaptive radiation therapy: a tool for deformable image registration assessment and re-planning indication. *Physics in Medicine and Biology 58*, 287-299 (2013). DOI: 10.1088/0031-9155/58/2/287
28. Paganelli C, Peroni M, Pennati F, Baroni G, Summers P, Bellomi M & Riboldi M. Scale invariant feature transform as feature tracking method in 4D imaging: a feasibility study. *Conference proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference 2012*, 6543-6546 (2012). DOI: 10.1109/embc.2012.6347493
29. Ciardo D, Peroni M, Riboldi M, Alterio D, Baroni G & Orecchia R. The role of regularization in deformable image registration for head and neck adaptive radiotherapy. *Technology in Cancer Research & Treatment 12*, 323-331 (2013). DOI: 10.7785/tcrt.2012.500327
30. Hild S, Durante M & Bert C. Assessment of uncertainties in treatment planning for scanned ion beam therapy of moving tumors. *International Journal of Radiation Oncology Biology Physics 85*, 528-535 (2013). DOI: 10.1016/j.ijrobp.2012.04.011
31. Lüchtenborg R. Real-time Dose Compensation Methods for Scanned Ion Beam Therapy of Moving Tumors, Ph.D. thesis, Technical University Darmstadt (2012).
32. Trofimov A, Rietzel E, Lu HM, Martin B, Jiang S, Chen GTY & Bortfeld T. Temporo-spatial IMRT optimization: concepts, implementation and initial results. *Physics in Medicine and Biology 50*, 2779-2798 (2005). PMID: 15930602
33. Suh Y, Weiss E, Zhong H, Fatyga M, Siebers JV & Keall PJ. A deliverable four-dimensional intensity-modulated radiation therapy-planning method for dynamic multileaf collimator tumor tracking delivery. *International Journal of Radiation Oncology, Biology, Physics 71*, 1526-1536 (2008). DOI: 10.1016/j.ijrobp.2008.04.018
34. Suh Y, Sawant A, Venkat R & Keall PJ. Four-dimensional IMRT treatment planning using a DMLC motion-tracking algorithm. *Phys Med Biol 54*, 3821-3835 (2009). DOI: 10.1088/0031-9155/54/12/014
35. Knopf A-C, Boye D, Lomax A & Mori S. Adequate margin definition for scanned particle therapy in the incidence of intrafractional motion. *Physics in Medicine and Biology 58*, 6079-6094 (2013). DOI: 10.1088/0031-9155/58/17/6079
36. Knopf A, Zenklusen S & Lomax T. in *Dreiländertagung* (Wien, 2011).
37. Eley J, Graeff C, Luechtenborg R, Durante M, Howell R, Newhauser W & Bert C. 4D optimization for scanned ion beam tracking therapy for moving tumors. *Medical Physics 39*, 3970-3970 (2012).
38. Graeff C, Lüchtenborg R, Eley J, Durante M & Bert C. in *PTCOG 52* (Essen, 2013).
39. van't Riet A, Mak AC, Moerland MA, Elders LH & van der Zee W. A conformation number to quantify the degree of conformality in brachytherapy and external beam irradiation: application to the prostate. *Int J Radiat Oncol Biol Phys 37*, 731-736 (1997). PMID:9112473
40. Bert C, Groezinger SO & Rietzel E. Quantification of interplay effects of scanned particle beams and moving targets. *Physics in Medicine and Biology 53*, 2253-2265 (2008). DOI: 10.1088/0031-9155/53/9/003
41. Schätti A, Zakova M, Meer D & Lomax T. OC-0058 experimental verification of rescanning and gating for moving tumours with fast proton spot scanning. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology 103*, S23 (2012).
42. Gemmel A, Bert C, Saito N, von Neubeck C, Iancu G, K-Weyrather W, Durante M & Rietzel E. Development and performance evaluation of a dynamic phantom for biological dosimetry of moving targets. *Physics in Medicine and Biology 55*, 2997-3009 (2010). DOI: 10.1088/0031-9155/55/11/001
43. Stutzer K, Bert C, Enghardt W, Helmbrecht S, Parodi K, Priegnitz M, Saito N & Fiedler F. Experimental verification of a 4D MLEM reconstruction algorithm used for in-beam PET measurements in particle therapy. *Physics in Medicine and Biology 58*, 5085-5111 (2013). DOI: 10.1088/0031-9155/58/15/5085
44. Luchtenborg R, Saito N, Durante M & Bert C. Experimental verification of a real-time compensation functionality for dose changes due to target motion in scanned particle therapy. *Medical Physics 38*, 5448-5458 (2011). DOI: 10.1118/1.3633891
45. Zakova M, Schätti A, Knopf A, Safai S, Meer D, Zhang Y, Boye D, Lomax T & Tiefenauer R. Breathing antropomorphic thorax phantom for experimental studies of moving tumors in proton therapy. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology 103*, S314 (2012).

46. Steidl P, Richter D, Schuy C, Schubert E, Haberer T, Durante M & Bert C. A breathing thorax phantom with independently programmable 6D tumour motion for dosimetric measurements in radiation therapy. *Physics in Medicine and Biology 57*, 2235-2250 (2012). DOI: 10.1088/0031-9155/57/8/2235
47. Seregni M, Kaderka R, Fattori G, Riboldi M, Pella A, Constantinescu A, Saito N, Durante M, Cerveri P, Bert C & Baroni G. Tumor tracking based on correlation models in scanned ion beam therapy: an experimental study. *Physics in Medicine and Biology 58*, 4659-4678 (2013). DOI: 10.1088/0031-9155/58/13/4659
48. Bert C, Gemmel A, Saito N & Rietzel E. Gated irradiation with scanned particle beams. *International Journal of Radiation Oncology*Biology*Physics 73*, 1270-1275 (2009). DOI: 10.1016/j.ijrobp.2008.11.014
49. Bert C, Saito N, Schmidt A, Chaudhri N, Schardt D & Rietzel E. Target motion tracking with a scanned particle beam. *Medical Physics 34*, 4768-4771 (2007). DOI: 10.1118/1.2815934
50. Gemmel A, Rietzel E, Kraft G, Durante M & Bert C. Calculation and experimental verification of the RBE-weighted dose for scanned ion beams in the presence of target motion. *Physics in Medicine and Biology 56*, 7337-7351 (2011). DOI: 10.1088/0031-9155/56/23/001
51. Enghardt W, Debus J, Haberer T, Hasch BG, Hinz R, Jäkel O, Kramer M, Lauckner K & Pawelke J. The application of PET to quality assurance of heavy-ion tumor therapy. *Strahlentherapie und Onkologie 175*(Suppl 2), 33-36 (1999). PMID:10394393
52. Laube K, Menkel S, Bert C, Enghardt W, Helmbrecht S, Saito N & Fiedler F. 4D particle therapy PET simulation for moving targets irradiated with scanned ion beams. *Physics in Medicine and Biology 58*, 513-533 (2013). DOI: 10.1088/0031-9155/58/3/513
53. Riboldi M, Gionoli C, Spadea M, Travaini L, Ferrari M, Orrechia R, Cavedon C & Baroni G. in *ESTRO*. S391.
54. Gianoli C, Fontana G, Riboldi M, Cavedon C & Baroni G. 174 oral enhanced 4D PET optimization based on 4D CT motion modeling. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology 99*, S67-S68 (2011).
55. Yun J, Wachowicz K, Mackenzie M, Rathee S, Robinson D & Fallone BG. First demonstration of intrafractional tumor-tracked irradiation using 2D phantom MR images on a prototype linac-MR. *Medical Physics 40* (2013). DOI: 10.1118/1.4802735
56. Evans PM. Anatomical imaging for radiotherapy. *Physics in Medicine and Biology 53*, R151-R191 (2008). DOI: 10.1088/0031-9155/53/12/R01
57. Shirato H, Oita M, Fujita K, Watanabe Y & Miyasaka K. Feasibility of synchronization of real-time tumor-tracking radiotherapy and intensity-modulated radiotherapy from viewpoint of excessive dose from fluoroscopy. *International Journal of Radiation Oncology*Biology*Physics 60*, 335-341 (2004). PMID: 15337573
58. Ng JA, Booth J, Poulsen P, Kuncic Z & Keall PJ. Estimation of effective imaging dose for kilovoltage intratreatment monitoring of the prostate position during cancer radiotherapy. *Physics in Medicine and Biology 58*, 5983-5996 (2013). DOI: 10.1088/0031-9155/58/17/5983
59. Zhang Y, Zakova M, Knopf AK, Safai S & Lomax T. OC-0059 intrafractional online motion targeting – beam's eye view imaging system for scanned proton therapy. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology 103*, S23 (2012).
60. Zhang Y, Knopf A, Tanner C, Boye D & Lomax A. Deformable motion reconstruction for scanned proton beam therapy using on-line x-ray imaging. *Physics in Medicine and Biology Submitted* (2013).
61. Schaerer J, Fassi A, Riboldi M, Cerveri P, Baroni G & Sarrut D. Multi-dimensional respiratory motion tracking from markerless optical surface imaging based on deformable mesh registration. *Physics in Medicine and Biology 57*, 357-373 (2012). DOI: 10.1088/0031-9155/57/2/357
62. Prall M, Kaderka R, Saito N, Schwaab J, Sarti C, Parodi K, Bert C, Graeff C, Durante M & Jenne J. Ion beam tracking using ultrasound motion detection. *Medical Physics Submitted* (2013).
63. Schmitt D, Nill S, Roeder F, Herth F & Oelfke U. Quantification of intrafractional tumor motion in the upper lung using an electromagnetic tumor tracking system. *Medical Physics 40*, 412 (2013).
64. Shah AP, Kupelian PA, Waghorn BJ, Willoughby TR, Rineer JM, Manon RR, Vollenweider MA & Meeks SL. Real-time tumor tracking in the lung using an electromagnetic tracking system. *Int J Radiat Oncol Biol Phys 86*, 477-483 (2013). DOI: 10.1016/j.ijrobp.2012.12.030
65. Willoughby TR, Kupelian PA, Pouliot J, Shinohara K, Aubin M, Roach M, 3rd, Skrumeda LL, Balter JM, Litzenberg DW, Hadley SW, Wei JT & Sandler HM. Target localization and real-time tracking using the Calypso 4D localization system in patients with localized prostate cancer. *Int J Radiat Oncol Biol Phys 65*, 528-534 (2006). DOI: 10.1016/j.ijrobp.2006.01.050
66. CalypsoMedical. <http://www.calypsomedical.com/press-release/calypso-medical-installs-system-world%E2%80%99s-largest-proton-facility-university-pennsylvani> (2011).
67. Krauss A, Nill S & Oelfke U. The comparative performance of four respiratory motion predictors for real-time tumour tracking. *Phys Med Biol 56*, 5303-5317 (2011). DOI: 10.1088/0031-9155/56/16/015
68. Torshabi AE, Pella A, Riboldi M & Baroni G. Targeting accuracy in real-time tumor tracking via external surrogates: a comparative study. *Technol Cancer Res Treat 9*, 551-562 (2010). PMID: 21070077
69. Seregni M, Cerveri P, Riboldi M, Pella A & Baroni G. Robustness of external/internal correlation models for real-time tumor tracking to breathing motion variations. *Physics in Medicine and Biology 57*, 7053-7074 (2012). DOI: 10.1088/0031-9155/57/21/7053
70. Torshabi AE, Riboldi M, Fooladi AAI, Mosalla SMM & Baroni G. An adaptive fuzzy prediction model for real time tumor tracking in radiotherapy via external surrogates. *Journal of Applied Clinical Medical Physics 14*, 102-114 (2013). DOI: 10.1120/jacmp.v14i1.4008
71. Steward VW & Koehler AM. Proton radiographic detection of strokes. *Nature 245*, 38-40 (1973). DOI: 10.1038/245038a0
72. Schneider U & Pedroni E. Proton radiography as a tool for quality control in proton therapy. *Medical Physics 22*, 353-363 (1995). PMID: 7609715
73. Rinaldi I, Brons S, Gordon J, Panse R, Voss B, Jaekel O & Parodi K. Experimental characterization of a prototype detector system for carbon ion radiography and tomography. *Physics in Medicine and Biology 58*, 413-427 (2013). DOI: 10.1088/0031-9155/58/3/413
74. Telsemeyer J, Jaeakel O & Martisikova M. Quantitative carbon ion beam radiography and tomography with a flat-panel detector. *Physics in Medicine and Biology 57*, 7957-7971 (2012). DOI: 10.1088/0031-9155/57/23/7957
75. Spadea M, Fassi A, Depauw N, Riboldi M, Baroni G & Seco J. Contrast enhanced proton radiography for in-room soft tissue-based setup. *International Journal of Radiation Oncology Biology Physics 84*, S53-S53 (2012).
76. Spadea M, Fassi A, Depauw N, Riboldi M, Baroni G & Seco J. Improving the contrast of proton and carbon radiography by using CT prior knowledge. *Medical Physics 39*, 4012-4012 (2012).
77. ICRU. ICRU Report 62: Prescribing, Recording and Reporting Photon Beam Therapy (International Commission on Radiation Units and Measurements, Bethesda, Md, USA, 1999).
78. ICRU. ICRU Report 78: Prescribing, recording and reporting proton-beam therapy. *Journal of the ICRU 7*, 1-210 (2007).
79. Koto M, Miyamoto T, Yamamoto N, Nishimura H, Yamada S & Tsujii H. Local control and recurrence of stage I non-small cell lung cancer after carbon ion radiotherapy. *Radiotherapy and Oncology 71*, 147-156 (2004). PMID: 15110447
80. Engelsman M, Rietzel E & Kooy HM. Four-dimensional proton treatment planning for lung tumors. *Int J Radiat Oncol Biol Phys 64*, 1589-1595 (2006). PMID: 16580508

81. Bert C & Rietzel E. 4D treatment planning for scanned ion beams. *Radiation Oncology 2* (2007). DOI: 10.1186/1748-717x-2-24
82. Rietzel E & Bert C. Respiratory motion management in particle therapy. *Medical Physics 37*, 449-460 (2010). PMID: 20229853
83. Graeff C, Durante M & Bert C. Motion mitigation in intensity modulated particle therapy by internal target volumes covering range changes. *Medical Physics 39*, 6004-6013 (2012). DOI: 10.1118/1.4749964
84. Phillips MH, Pedroni E, Blattmann H, Boehringer T, Coray A & Scheib S. Effects of respiratory motion on dose uniformity with a charged particle scanning method. *Physics in Medicine and Biology 37*, 223-233 (1992). PMID: 1311106
85. Seco J, Robertson D, Trofimov A & Paganetti H. Breathing interplay effects during proton beam scanning: simulation and statistical analysis. *Phys Med Biol 54*, N283-N294 (2009). DOI: 10.1088/0031-9155/54/14/N01
86. Zenklusen SM, Pedroni E & Meer D. A study on repainting strategies for treating moderately moving targets with proton pencil beam scanning at the new Gantry 2 at PSI. *Phys Med Biol 55*, 5103-5121 (2010). DOI: 10.1088/0031-9155/55/17/014
87. Bernatowicz K, Lomax A & Knopf A. Comparative study of layered and volumetric rescanning for scanned proton beam therapy. *Physics in Medicine and Biology Submitted* (2013).
88. Woelfelschneider J, Friedrich T, Graeff C, Zink K, Durante M & Bert C. Fractionated irradiation of moving tumours with scanned carbon ions. *Strahlentherapie Und Onkologie 188*, 12-12 (2012).
89. Furukawa T, Inaniwa T, Sato S, Shirai T, Takei Y, Takeshita E, Mizushima K, Iwata Y, Himukai T, Mori S, Fukuda S, Minohara S, Takada E, Murakami T & Noda K. Performance of the NIRS fast scanning system for heavy-ion radiotherapy. *Med Phys 37*, 5672-5682 (2010). PMID:21158279
90. van de Water S, Kreuger R, Zenklusen S, Hug E & Lomax AJ. Tumour tracking with scanned proton beams: assessing the accuracy and practicalities. *Phys Med Biol 54*, 6549-6563 (2009). DOI: 10.1088/0031-9155/54/21/007
91. Minohara S, Kanai T, Endo M, Noda K & Kanazawa M. Respiratory gated irradiation system for heavy-ion radiotherapy. *International Journal of Radiation Oncology*Biology*Physics 47*, 1097-1103 (2000). PMID: 10863083
92. Steidl P. Gating for Scanned Ion Beam Therapy PhD thesis, TU Darmstadt (2012).
93. Richter D. *Treatment Planning for Tumors with Residual Motion in Scanned ion Beam Therapy* Ph.D. thesis, Technical University Darmstadt (2012).
94. Steidl P, Haberer T, Durante M & Bert C. Gating delays for two respiratory motion sensors in scanned particle radiation therapy. *Physics in Medicine and Biology* in print (2013).
95. Chaudhri N, Richter D, Haertig M, Ecker S, Ackermann B, Naumann J, Haberer T, Bert C, Habermehl D, Herfarth K, Ellerbrock M & Jaekel O. Clinical implementation of gating and dose verification with scanned ion beams at HIT. *Med Phys 39*, 3780-3781 (2012).
96. Richter D, Saito N, Chaudhri N, Härtig M, Ellerbrock M, Jäkel O, Combs S, Habermehl D, Herfarth K, Durante M & Bert C. 4D patient dose reconstruction for scanned ion beam therapy of moving liver tumors. *International Journal of Radiation Oncology*Biology*Physics Submitted* (2013).
97. Grözinger SO, Rietzel E, Li Q, Bert C, Haberer T & Kraft G. Simulations to design an online motion compensation system for scanned particle beams. *Physics in Medicine and Biology 51*, 3517-3531 (2006). PMID: 16825746
98. Saito N, Bert C, Chaudhri N, Gemmel A, Schardt D, Durante M & Rietzel E. Speed and accuracy of a beam tracking system for treatment of moving targets with scanned ion beams. *Physics in Medicine and Biology 54*, 4849-4862 (2009). DOI: 10.1088/0031-9155/54/16/001
99. Grözinger SO, Bert C, Haberer T, Kraft G & Rietzel E. Motion compensation with a scanned ion beam: a technical feasibility study. *Radiation Oncology 3* (2008). DOI: 10.1186/1748-717X-3-34
100. Bert C, Gemmel A, Saito N, Chaudhri N, Schardt D, Durante M, Kraft G & Rietzel E. Dosimetric precision of an ion beam tracking system. *Radiat Oncol 5*, 61 (2010). DOI: 10.1186/1748-717X-5-61
101. Wölfelschneider J, Friedrich T, Lüchtenborg R, Zink K, Scholz M, Dong L, Durante M & Bert C. Fractionated treatment of intrafractionally moving tumors with scanned carbon ions. *International Journal of Radiation Oncology Biology Physics Submitted* (2013).
102. Bortfeld T, Jokivarsi K, Goitein M, Kung J & Jiang SB. Effects of intra-fraction motion on IMRT dose delivery: statistical analysis and simulation. *Phys Med Biol 47*, 2203-2220 (2002). PMID: 12164582
103. Okada T, Kamada T, Tsuji H, Mizoe JE, Baba M, Kato S, Yamada S, Sugahara S, Yasuda S, Yamamoto N, Imai R, Hasegawa A, Imada H, Kiyohara H, Jingu K, Shinoto M & Tsujii H. Carbon ion radiotherapy: clinical experiences at National Institute of Radiological Science (NIRS). *Journal of Radiation Research 51*, 355-364 (2010). PMID: 20508375

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