Physica Medica 57 (2019) 215–220

Contents lists available at ScienceDirect

Physica Medica

journal homepage: www.elsevier.com/locate/ejmp

Original paper

Implementation of proton therapy treatments with pencil beam scanning of targets with limited intrafraction motion

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ARTICLE INFO

Keywords:
Proton therapy
Moving target
Interplay effect

ABSTRACT

Purpose: To report on the implementation, validation and results of the first two proton therapy PBS treatments of limited amplitudes moving targets performed at our center.
Methods and materials: A real time optical tracking system was used to monitor the patient surface during the CT scan and treatment. This system is also able to trigger the beam during the treatment. A 4DCT (10 phases) and a Free-Breathing CT (FBCT) were used for the planning. The physician used the 4DCT for ITV delineation, while planning was performed on the FBCT. The approved plan was evaluated in two ways:

- dose recalculation on each 4DCT phase.
- Interplay effect evaluation: every spot was assigned to a phase according to the beam delivery time and the breathing curve of the patient. The 10 doses were then deformed and summed on the FBCT.

The largest breathing amplitude recorded during 4DCT scan was used as gating safety threshold during treatment delivery.

This planning and treatment workflow was then applied for two patients affected by thoracic thymoma.
Results: The dosimetric evaluation of the plan showed no interplay effect. The second patient showed an overdosage to the coronary and Left Anterior Descending area in the worst case scenario but it was below the constraints. Duty Cycle together with number of beam interruptions gave information about the patient compliance to the treatment: the first patient breath is stable and within thresholds, whilst the second patient had more variations, causing multiple beam interruptions.
Conclusion: We defined and used for two patients a protocol for the treatment of small amplitude moving targets. The planning and delivery of the treatments gave very good results in terms of coverage, OARs sparing, 4D dose evaluation of the plan and interplay effect assessment.

1. Introduction

Pencil beam scanning (PBS) is the most common delivery technique in proton therapy nowadays because of its high potential to reach good dose homogeneity to the target and organs at risk (OAR) sparing. It is possible to modulate each beam in terms of position, intensity and energy to reach the best plan quality. In case of static lesions, the quality of the dose distribution can be more easily ensured as long as position and range uncertainty are taken into account. For moving targets the intra-fraction anatomy changes can have a great impact on the dose distribution [1]. This is true for any type of external beam radiotherapy because the anatomy being treated is not the same as the one used during the planning [2–4].

In PBS proton therapy treatments the active delivery system adds another source of uncertainty to the final dose distribution: the active delivery and the movement of the target can lead to an interplay effect [5–8]. This effect is more evident when the delivery time structure is on the same scale as the organ motion. The interplay effect is more severe for pencil beam scanning treatments because of the high gradient dose distributions achievable with ions respect with modulated photon radiotherapy and the resulting dose distortion can be clinically unacceptable.

There are different methods to reduce the interplay effect. In 2011 Bert and Durante [8] gave a complete review of all possible methods

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https://doi.org/10.1016/j.ejmp.2019.01.007
Received 2 August 2018; Received in revised form 7 January 2019; Accepted 8 January 2019
Available online 17 January 2019

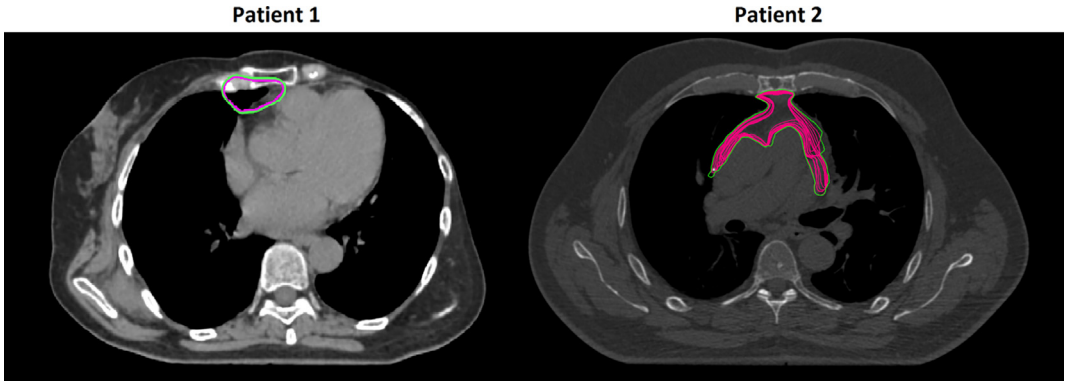

Fig. 1. Purple contours represent the CTVs copied from each phase of the 4DCT to the FBCT. The green contour is the ITV. Patient 1 on the left, patient 2 on the right. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

available nowadays. These methods can be distinguished into two classes: motion mitigation techniques and dose distortion mitigation techniques. The former, like abdominal compression [9] and breath-hold [10], are aimed at reducing the organ motion in order to eliminate one of the sources of the interplay effect. The latter, like beam gating [11,12], rescanning [6,13], beam tracking [14,15], spot size variations [16] etc., are aimed at modifying the beam characteristics in order to reduce the effect on the dose due to the active delivery.

A combination of these methods can be used to mitigate the interplay effect [17]. Both of these class bring with them some negative effects. For example, motion mitigation techniques can be uncomfortable for the patient and it must be verified if the patient can comply with these procedures before starting the treatment workflow. Dose distortion mitigation techniques have an impact on the treatment duration and this could conflict with the scheduling of the treatments (especially in a multi-gantry facility) or with the patient compliance. Typically the formers are the first used in a proton therapy facility to mitigate the interplay effect because the commissioning time and the definition of the procedures are faster and more easy to implement.

If the movement is small enough, it is possible to treat moving target in free-breathing. This is possible when a tool for the evaluation of the effect of the anatomy changes and of the interplay effect on the dose distribution is available. In our center the first patients with moving targets treated were those with lesion located in the mediastinum and at shallow depths. For these patients, we acquired a free-breathing CT for the planning and a 4DCT for a complete description of the anatomy changes during the breathing period. Beam directions are chosen in such a way to minimize the impact of breathing motion: the main motion direction for these lesions close to the chest wall was the anterior-posterior direction. We chose anterior beams in order to reduce the impact of the movement on the dose degradation. Once the nominal plan is approved, the effect of anatomy changes on the dose distribution is evaluated by recalculating the plan on each phase of the 4DCT. In addition, an in-house developed script allows for an estimation of the interplay effect by combining the delivery times and the patient breathing curve information. These evaluation scenarios are valid as long as the breathing pattern of the patient during imaging and treatment are as similar as possible. In order to ensure this, we treated these patients by monitoring their breathing and by using a gating window as large as the maximum breathing amplitude acquired during the 4DCT.

This paper has the aim to share the workflow developed in our center to treat small amplitudes moving targets treated in free breathing from imaging to dose reporting to treatment delivery.

2. Materials and methods

The Pencil Beam Scanning (PBS) delivery system in Trento is an IBA cyclotron-based facility with two isocentric gantry rooms and a fixed line. The energies available vary continuously from 70 to 226 MeV (4.0–32.5 g/cm^2 in terms of range). The characterization of the PBS system has been described elsewhere [18]. The TPS used is Raystation 6.0 (RAYSEARCH, Stockholm) with a Monte Carlo dose calculation algorithm [19].

Two patients affected by thymoma were selected for this study. The volume of each PTV was 86.08 cc and 447.51 cc, respectively. The OAR evaluated were the heart, heart's sub-volumes (i.e. RCA, LAD and coronary) and the lung. The first was a 68 year old female while the second a 67 years old male. The prescription was 66GyRBE delivered in 33 fractions for the first patient (2.0 GyRBE/fraction) and 54 GyRBE in 30 fractions (1.8 GyRBE/fraction) for the second. The first patient had a maximum depth of 4.2 cm while the second 12.3 cm.

The optical tracking system used was VisionRT (http://www.visionrt.com/). It was used for both imaging and treatment delivery. The system monitors a point on the patient surface during the CT acquisition and the breathing signal is used for image reconstruction. The infrared ray reflected by the patient surface is used to monitor the amplitude of the breathing motion (expressed in mm) and it is the result of an average of the motion over a rectangular ROI that can be reduced or enlarged as needed by the user. The same ROI selected during the 4DCT for the monitoring was used (in terms of area and position) for the monitoring during the treatment delivery.

For both patients a Free-Breathing CT (FBCT) and a 4DCT were acquired. Each CT was calibrated with its own calibration curve in order to reduce the variability of HU to density conversion due to the use of different CT acquisition protocol. The 4DCT was reconstructed with an amplitude reconstruction method with ten phases [20–22]. Every phase was rigidly and deformable registered [23] with the FBCT that was used as planning CT. The Internal Target Volume (ITV) was created on the FBCT as the union of all CTVs contoured on each phase of the 4DCT. The motion of the target for the first patient was less than 2 mm in every phase of the 4DCT while for the second it was 8 mm. An image of the union of all CTVs for each patient is in Fig. 1. The PTV was obtained expanding the ITV of 5 mm. The deformable registration was used to map the OARs from the planning CT to every phase of the 4DCT in order to perform dose accumulation. After the mapping of each OARs the physician verified and, eventually, corrected the contours in every phase of the 4DCT.

The first patient was treated with two anterior beams: 10° and −30° with the couch at 0°, while the second with three beams: 20° and 340° of gantry angle with couch at 0°, and 330° of gantry angle with couch at 90°. The beam directions were chosen in such a way that the breathing motion was occurring mainly along the beam direction, as opposed to in the orthogonal direction, in order to minimize the possible dose perturbations due to breathing: with an anterior-posterior motion what changed was only the air-gap between the chest wall and the exit window of the nozzle; this variation had a reduced impact on the range

of each beam. The use of the third beam for the second patient was due to the fact that this patient had a superior-inferior component of the motion of his chest wall. The use of three beams for this patient helped to minimize the motion induced density variation effect for each field. Every beam was divided into two components: the shallower part of the tumor was treated with the range shifter, the deepest part without it to better spare the OAR located laterally close to the tumor since the range shifter degrades the lateral penumbra of the single pencil beam.

After approval of the nominal dose distribution, the plan is evaluated with two methods: worst case scenario and the interplay effect scenario. In the first case the whole plan is recalculated on each phase and each of the ten dose is evaluated in terms of target coverage and OAR sparing. The worst dose distribution represents the worst case scenario.

The interplay effect scenario was evaluated with an in-house developed script. The script assigns every spot to a given phase of the 4DCT according to breathing curve of the patient and the time delivery parameters (i.e. scan speed on X and Y direction, energy switching time and mean delivery time per spot) derived from the log files of the treatment machine. We derived also the beam current in the gantry room for each field and reported this parameter as a surrogate of the proton dose rate. Using the deformable registration performed previously, the ten dose distributions were deformed and summed on the planning CT in order to compare the nominal dose with the interplay effect scenario (4D Dose Distribution – 4DDD [24]).

The interplay evaluation script was also used to test the effect of choosing a different starting phase for the evaluation of the 4DDD and the impact of this choice on each OAR dose index and target coverage.

The dose distribution and the dose statistics for each ROI obtained from the interplay effect scenario are included in the patient plan report together with the nominal plan. The patient is cleared for treatment only if the dose distribution is deemed clinically acceptable also in the worst case scenario.

The system used to track the breathing pattern for the 4DCT reconstruction can be used for beam gating during the treatment. The patient surface acquired during 4DCT acquisition can be imported and matched with the surface-of-the-day acquired in treatment room. In this way the tracking point used for the imaging is the same point used during the delivery. The system has the possibility to stop the delivery if the patient exceed the maximum or minimum threshold set by the user. The thresholds used are based on the breathing curve of the patient during the 4DCT acquisition: the maximum amplitude registered during the 4DCT acquisition (with a safety margin of 2 mm) is used as gating window during the treatment. For example the breathing curve acquired during the imaging in Fig. 2 will give a gating window of 10 mm (8 mm of maximum breathing amplitude and 2 mm of safety margin). In this way if the breathing amplitude is different from what is being registered during the imaging (i.e. larger amplitude due to cough) the beam is automatically turned off.

For every FB treatment the Duty Cycle was calculated as the ratio between the beam-ON time and the gate-ON time. The gate-ON time is intended as the time the gating system was active. We also looked at the number of interruptions e.g. the number of times that the breathing signal was beyond the thresholds. These two parameters were evaluated to study the compliance of the patient during the treatment and the stability and reproducibility of their breathing cycle. Lastly a statistical analysis of the breathing period of each patient was performed. The minimum and maximum value of the period registered was used to calculate a 4DDD and compared with the nominal dose distribution in order to evaluate, retrospectively, the effect of different breathing period registered during the treatment on the plan quality.

3. Results

In Table 1 a summary of the planning results, compared with worst case and interplay effect scenario's results, is shown in terms of target coverage and OAR's clinical goals. The second patient showed an over dosage to the coronary and Left Anterior Descending area but it was always below the constraints. In both patients no interplay effect was highlighted. An example of 4DDD determined for the first patient is shown in Fig. 3.

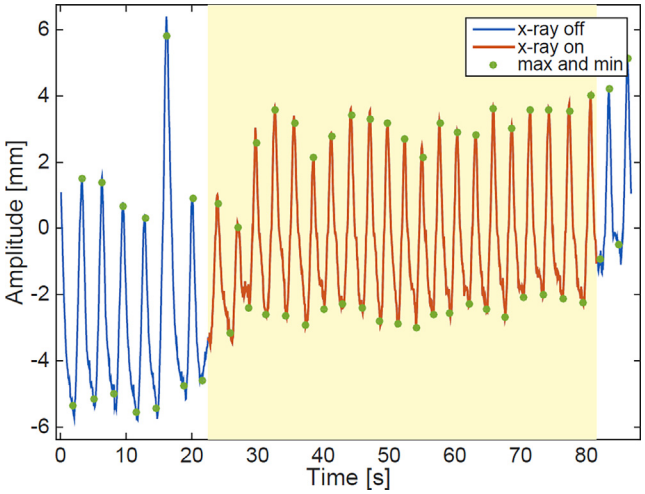

Fig. 2. Patient breathing curve during the acquisition of the 4DCT. The yellow area is the X-ray on time and the signal in this area was used for 4DCT retrospective reconstruction. The green points are the minimum and maximum automatically recognized by the tracking system. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In Table 2 there is a summary of the beam parameters in terms of delivery time derived from the log files of the treatment of each patient: scan speed, energy switching time, dead time between two spots and mean delivery time per spot. These parameters were used for each patient in the interplay effect evaluation tool. In the last three columns of the table the beam current in the gantry room (maximum, minimum and mean value) was reported. This value was derived from the extraction current at the cyclotron corrected for the transmission efficiency as a function of the beam energy.

In Table 3 a summary of the dose index variations is presented as a function of the starting phase used for the interplay effect calculation. In the last two columns there are the mean value and the standard deviation, expressed as a percentage of the mean value, of each dose index in the table. For the first patient no dose index varies more than 1% while for the second the maximum variation is 1.76%. In no case the dose index violated the planning constraints in Table 1.

In Fig. 4 there is an example of the breathing curve of each patient during the treatments. The yellow areas represent the time during which the gating system was activated (gate on time). The horizontal dotted lines are the threshold selected for each patient: the beam is on only when the breathing pattern is in between these two lines. The breathing curve of the second patient was more irregular and a lot of pauses were detected during the treatments. In particular in Table 4 the duty cycle and the statistics of number of interruptions for each patient is reported.

The analysis on the breathing curves at the end of the treatment showed that for the first patient the period was 3.3 ± 0.5 s (mean ± SD) while the second 4.0 ± 1.0 s. The interplay effect evaluation of each plan with the minimum and maximum value of these intervals showed that no dose index varied more than 1%.

4. Discussion

In this study we proposed a method to implement the safe treatment of small amplitudes moving targets. Mediastinal lesions (thymomas, lymphomas etc.) are eligible for this workflow because the amplitude of

Table 1
Dose indexes of the two patients treated. RCA = Right Coronary Artery, LAD = Left Anterior Descending, ITV = Internal Target Volume.

Patient ID		Dose Parameters				
	ROI	Dose index	Planning constraints	Nominal plan	worst case scenario	interplay effect
1	Area RCA	D1 (GyRBE)	54,00	63,44	64,78	63,69
	Heart	V20GyRBE (%)	5,00	4,96	5,37	5,62
	Lung	V20GyRBE (%)	20,00	4,28	4,64	4,52
	ITV	D98 (GyRBE)	62,70	58,40	59,11	59,07
		D1 (GyRBE)	69,30	68,83	68,77	68,13
2	Area LAD	D1 (GyRBE)	54,00	51,29	53,32	53,75
	Heart	V20GyRBE (%)	5,00	27,75	27,67	27,02
	Coronary	D1 (GyRBE)	54,00	51,02	54,24	50,67
	Left Lung	V20GyRBE (%)	20,00	11,79	15,80	12,75
	Right Lung	V20GyRBE (%)	20,00	12,45	16,41	13,63
	ITV	D98 (GyRBE)	51,30	49,66	48,49	50,07
		D1 (GyRBE)	56,70	55,29	55,32	55,93

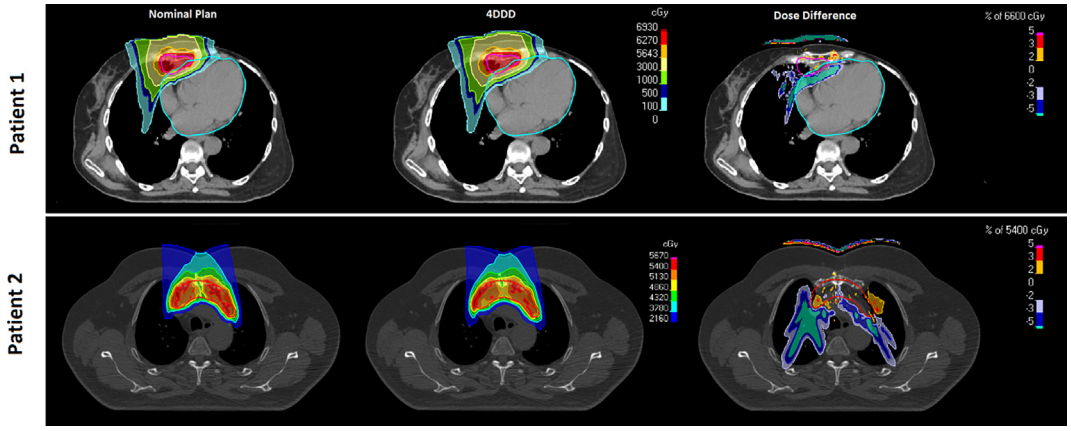

Fig. 3. An example of comparison, for both patients, between nominal dose (left) and interplay effect dose evaluation (middle). The dose difference (Nominal Plan – 4DDD) is shown on the right. The dose differences are normalized to the prescription dose of every patient.

Table 2
. Spot delivery time parameters derived from the log file of each patient treatment. These parameters were used to evaluate the interplay effect scenario.

Patient	Scan speed (cm/s)		Energy switching time (s)		Dead time between spots (ms)		Mean delivery time per spot (ms)		Beam current at gantry room (nA)		
	Min	Max	Mean	SD	Mean	SD	Mean	SD	Max	Min	Mean
1	85.03	238.10	1.28	0.13	3.41	3.66	2.77	1.06	3.93	0.69	2.34
2	17.89	112.11	1.37	0.11	11.07	9.46	1.96	0.39	8.91	0.27	2.27

site movement is usually limited. If anterior fields are used to treat those lesions the movement is longitudinal to the beam direction and the impact on the dose distribution is likely to be acceptable. Nonetheless, every time a moving target is evaluated for treatment with particle therapy an interplay evaluation tool available is a necessary condition to start the treatment itself [13].

We proposed a workflow, from imaging to treatment delivery, that may help upcoming proton therapy centers that want to start the treatment of these lesions.

We showed that the imaging is a crucial step to ensure the best plan quality for the patient. The breathing curve acquired during the 4DCT is a guideline for the gating threshold definition during the treatment delivery: during planning evaluation every phase of the 4DCT is used to recalculate the plan to find the worst case scenario. This means that the plan quality is evaluated only in those scenarios contemplated in the 4DCT scan acquisition. Every breathing amplitude greater or lower than the one acquired during the imaging generate scenarios that cannot be evaluated with the TPS, so they have to be excluded during the treatment delivery by triggering the beam with a gating system (in our case an optical tracking system).

We used the log files of the irradiations to evaluate the interplay effect scenario. The analysis of the log files showed that during the irradiation the mean dead time between the delivery of two consecutive spots is always higher than the mean delivery time of the spots. This means that the dead time has a large impact on the treatment time and it needs to be taken into account for the interplay effect evaluation. The dead time distribution is very broad (the standard deviation is comparable with the mean value) because the distance between spots can be small or large depending on how the TPS arrange them during the optimization.

The two patients selected for this study showed that the plan was robust when both the worst case scenario and the interplay effect were evaluated (see Table 1). This happened even if the breathing pattern of two patients was very different (see Fig. 4): the first patient had a more stable and reproducible breathing curve while the second had very large amplitude variations that led to several beam interruptions during the treatment (see Table 4).

In this study we tested also if, with the same breathing and delivery time parameters, the starting phase has an impact on the 4DDD. Both plans showed to be robust with respect the variation of this parameter

Table 3
. Dose index evaluation with respect the variation of the starting phase for the calculation of the 4D Dose Distribution. SD is the standard deviation expressed as a percentage of the mean value.

Patient 1			Starting Phase										
ROI	Dose Index	Unit	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	Mean	SD (%)
RCA Area	D1	cGy	6222	6338	6404	6355	6400	6404	6332	6409	6424	6381	6367	0.94%
Heart	V20	%	5.30	5.33	5.36	5.33	5.34	5.33	5.36	5.32	5.33	5.36	5.34	0.37%
Lung	V20	%	4.46	4.49	4.46	4.46	4.51	4.45	4.48	4.45	4.43	4.45	4.46	0.52%
ITV	D98	cGy	5817	5813	5802	5826	5817	5735	5740	5807	5814	5816	5799	0.57%
	D1	cGy	6812	6833	6808	6790	6823	6820	6810	6846	6835	6859	6824	0.30%
Patient 2			Starting Phase										
ROI	Dose Index	Unit	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	Mean	SD (%)
LAD Area	D1	cGy	5441	5377	5347	5290	5232	5291	5305	5332	5350	5308	5327	1.07%
Heart	V20	%	27.08	26.99	26.89	26.82	26.96	26.80	26.97	26.86	26.83	27.08	26.93	0.38%
Coronary	D1	cGy	5070	5039	4988	5055	5056	5140	5053	5180	5248	5242	5107	1.76%
Left Lung	V20	%	12.93	12.78	12.75	12.80	12.80	12.74	12.71	12.70	12.80	12.87	12.79	0.55%
Right Lung	V20	%	13.49	13.72	13.80	13.74	13.51	13.56	13.69	13.78	13.73	13.53	13.66	0.87%
ITV	D98	cGy	4929	4991	4979	4982	4964	4985	5002	4993	4970	4967	4976	0.41%
	D1	cGy	5581	5509	5490	5519	5530	5528	5545	5519	5537	5537	5530	0.44%

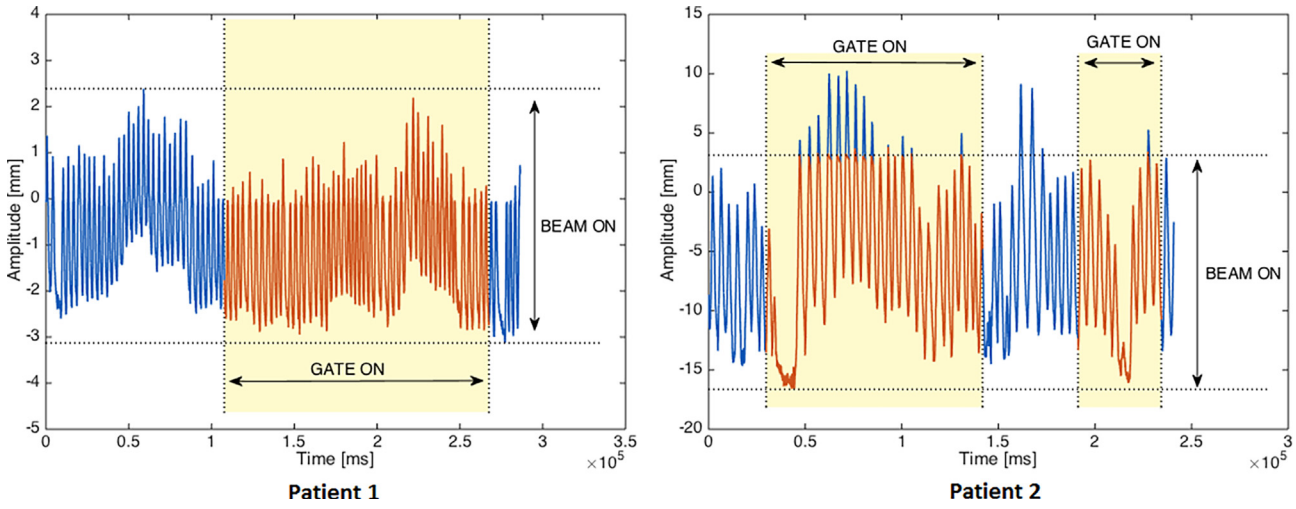

Fig. 4. Breathing curve of a patient obtained using VisionRT® during treatment. The highlighted yellow areas are the interval of time in which the gating system is activated (gate on). While the orange curve is showing the breathing pattern in which the patient could actually be irradiated (beam on region). The dotted horizontal lines are the gating threshold set for each patient. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4
. Statistical analysis of gated treatments in terms of duty cycle and number of breath holds.

Patient ID	Parameter	Average	Worst case
1	*Duty cycle*	98,18%	91,90%
	Number of beam hold	5,1	26
2	*Duty cycle*	94,85%	83,75%
	Number of beam hold	29,2	79

and no dose index varied more than 2% having no clinical impact. This evaluation has to be part of the evaluation of the plan because, during the treatment, the delivery of the beam does not start always with the same phase and the interplay effect can be different if the starting phase is not synchronized with the beam delivery.

The 4DDD of each plan was evaluated in a large number of scenarios: simulating different breathing periods of the patients, choosing all the phases as starting phase and recalculating the entire plan on each phase in order to select the worst case scenario. Every 4DDD was calculated on a single fraction and scaled to the total treatment dose: the mitigation effect on hot and cold spots due to the fractionation was not considered. The statistical analysis of the breathing period of each patient at the end of the treatment, the safety thresholds of our machine during the beam delivery (i.e. spot position threshold, energy selection system accuracy and monitor unit counter accuracy), the gating window to avoid large amplitude breathing pattern and the mitigation effect of the fractionation made us sure that our analysis considered the worst case scenarios and, in every scenario, it did not violate any planning constraints making the evaluation dose distribution always clinically acceptable. The 4DDD calculated with the real breathing curves and the log files would not give substantial differences with respect the 4DDD used for plan evaluation.

One of the source of uncertainty in 4DDD evaluation comes from the deformable image registration used to create the deformation vector field (DVF). The DVF is both used for contour propagation and for dose accumulation. In the workflow presented the goodness of contour propagation is verified in every phase of the 4DCT and, if needed, corrected by the clinician in order to correct any possible registration error. The dosimetric errors induced by deformable registration method should be assessed too. Ribeiro et al. [25] assessed the dosimetric error

induced by the ANACONDA algorithm and demonstrated that the DIR uncertainties can have a clinical impact on 4DDD. They concluded that dosimetric errors can be reduced and made clinically acceptable by using multiple fields, as we did in our clinical workflow, or by using rescanning as motion mitigation techniques. An a-posteriori statistical analysis on the breathing curves after the end of the treatment showed that the interval of variability of the period of each patient had no clinical relevant impact on the plan quality: each plan was recalculated with the interplay effect tool using the minimum and maximum value of each interval. No dose index had a clinical relevant variation.

For one of the two patients an additional imaging during the treatment was performed. This led to a new plan because of the significant volume reduction of the lesion. No additional imaging during the treatment was performed because the breathing pattern remained stable in terms of amplitude and period during the treatment.

5. Conclusions

We presented our method to start the treatment of small amplitude moving targets. We perform a double imaging (free-breathing CT and 4DCT) which are both used for volume definition and plan dose evaluation. In particular we highlighted the necessity to have an interplay evaluation tool to start the treatment of these type of lesions. The clinical cases presented showed that small amplitude moving targets treated have no interplay effect and the dose perturbation was small enough for the patients to be treated safely.

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