Received Date: 8 March 2016
Revised Date: 19 September 2016
Accepted Date: 6 October 2016

Title page

Proposed journal: Radiotherapy and Oncology

Title: Respiratory motion-management in stereotactic body radiation therapy for lung cancer - A dosimetric comparison in an anthropomorphic lung phantom (LuCa)

Running title: Respiratory motion-management in SBRT

Authors: Stefanie Ehrbar^{+1,2}, Rosalind Perrin³, Marta Peroni³, Kinga Bernatowicz³, Thomas Parkel⁴, Izabela Pytko^{1,2}, Stephan Klöck^{1,2}, Matthias Guckenberger^{1,2}, Stephanie Lang^{1,2}, Damien Charles Weber^{2,3}, Antony Lomax^{3,5}

Addresses:

¹ *Department of Radiation Oncology, University Hospital Zurich (USZ), Switzerland*

² *University of Zurich, Switzerland*

³ *Center for Proton Therapy, Paul Scherrer Institute (PSI), Switzerland*

⁴ *Innovative Design, Centre Suisse d'Electronique et de Microtechnique (CSEM) S. A., Switzerland*

⁵ *Swiss Federal Institute of Technology in Zurich (ETHZ), Switzerland*

⁺ *Corresponding author:* Department of Radiation Oncology
University Hospital Zurich
Rämistrasse 100
CH-8091 Zurich
+41 (0)44 255 1808
stefanie.ehrbar@usz.ch

Key words: Radiotherapy, couch tracking, respiratory motion management, stereotactic body radiation therapy, lung phantom

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as

doi: 10.1016/j.radonc.2016.10.011

This article is protected by copyright. All rights reserved.

Abstract

Background and Purpose: The objective of this study was to compare the latest respiratory motion-management strategies, namely the internal-target-volume (ITV) concept, the mid-ventilation (MidV) principle, respiratory gating and dynamic couch tracking.

Materials and Methods: An anthropomorphic, deformable and dynamic lung phantom was used for the dosimetric validation of these techniques. Stereotactic treatments were adapted to match the techniques and five distinct respiration patterns, and delivered to the phantom while radiographic film measurements were taken inside the tumor. To report on tumor coverage, these dose distributions were used to calculate mean doses (D_{mean}), changes in homogeneity indices (ΔH_{2-98}), gamma agreement, and areas covered by the planned minimum dose ($A_{>Dmin}$).

Results: All techniques achieved good tumor coverage ($A_{>Dmin} > 99.0\%$) and minor changes in D_{mean} ($\pm 3.2\%$). Gating and tracking strategies showed superior results in gamma agreement and ΔH_{2-98} compared to ITV and MidV concepts, which seem to be more influenced by the interplay and the gradient effect. For lung, heart and spinal cord, significant dose differences between the four techniques were found ($p < 0.05$), with lowest doses for gating and tracking strategies.

Conclusion: Active motion-management techniques, such as gating or tracking, showed superior tumor dose coverage and better organ dose sparing than the passive techniques based on tumor margins.

Introduction

The intra-fractional motion of lung tumors during radiotherapy treatment is strongly affected by respiration. Internal tumor motion larger than 30 mm in cranial-caudal direction has been reported [1]. This internal motion is a relevant uncertainty in radiotherapy, conventionally mitigated by extension of the target volume to cover the full motion envelope. As a consequence, this approach leads to higher radiation doses delivered to organs at risks (OARs). The management of respiratory motion, using breath-hold, beam gating or tracking techniques could lead to a desirable reduction in irradiation of OARs. In stereotactic body radiotherapy (SBRT), where high radiation doses are applied in a few fractions, this reduction might be beneficial to avoid increased toxicity to late-responding tissues associated with large fraction sizes.

The four main motion-management strategies under free breathing are the internal-target-volume (ITV) concept, the mid-ventilation (MidV) principle, respiratory gating, and dynamic target tracking. For the ITV concept [2], the whole extent of tumor motion is taken into the safety margin. This increases the target volume but ensures tumor coverage. In the MidV principle [3], the tumor motion is assumed to be a random position error of the tumor. The safety margins are based on probability calculations and added to the tumor volume in the MidV position, resulting in smaller treatment volumes than the ITV concept. Using a gating approach [4, 5], the tumor is only irradiated in a predefined respiratory window with a smaller range of motion. This technique leads to a reduction of irradiated volumes but increases overall treatment time. Lastly, dynamic target tracking is the continuous compensation of tumor motion by either following the motion with the treatment beam, or shifting the patient position according to their internal tumor motion, keeping the tumor at the treatment isocenter. Former is commercially realized in the robotic CyberKnife system [6] and the Vero gimbaled linac system [7, 8]. Alternatively to these specialized treatment systems, tracking can also be integrated at conventional linear accelerators, which are widely used in clinics. This can be accomplished by either adapting the multi-leaf collimator, which is shaping the treatment field, to the changing target position (MLC tracking) [9, 10, 11], or by counter-steering the target motion with the treatment couch (couch tracking) [12, 13]. Tracking allows for a reduction of the treatment volume with continuous irradiation. Both gating and tracking require real-time information on the tumor position, whereas the ITV concept and the MidV principle are both passive motion-management techniques based on the a priori extent of tumor motion.

Interplay and gradient effects also influence the dose delivered to moving targets. The moving tumor accumulates dose irregularly since, firstly, the tumor moves through the inhomogeneously planned SBRT dose (gradient effect) and secondly, the motion of the MLC leaves coupled with the continuous gantry rotation interferes with the target motion (interplay effect). These effects additionally could be reduced by gating the treatment to a steady tumor position or tracking the moving tumor.

Planning studies [14, 15, 8, 16] and phantom studies [17, 18] for comparisons between motion-management techniques have been performed previously. Planning studies are generally based on four-dimensional computed tomography data sets (4DCT), which provide patient-specific data for the dose calculation, but neglect actual capabilities of the delivery systems and are prone to motion artifacts [19]. The delivery capability of the techniques has only been reported in phantom studies with rigid, geometric phantoms. To date no study has compared all four techniques, nor has tumor coverage been considered as endpoint.

In the present study, SBRT treatments adapted to all of the above-mentioned respiratory motion-management techniques were delivered to an anthropomorphic, dynamic thorax phantom [20]. The four techniques were compared in respect to tumor coverage and OAR dose sparing.

Materials and Methods

The phantom

An anthropomorphic thorax phantom (LuCa) [20] was employed to simulate the anatomy and respiratory motion of a lung cancer patient (Figure 1). LuCa consists of an inflatable lung including a spherical wooden tumor (60 mm) with two coronal planes for film inserts at 20 and 40 mm depth, and fitted to the size of the rigid tumor. Around the lung are a tissue-equivalent ribcage and a skin layer. A heart model, containing a film insert, is placed within the lung. The inflation of the lung is controlled externally with a ventilator, which follows any desired respiration pattern and directly influences the cranial-caudal tumor motion. This study was focused on known regular motion patterns. The following five respiration patterns were chosen for this study: The ventilator was operated with four regular curves following a $\sin$ or $\sin^4$, with a respiratory cycle period of 4 seconds and internal peak-to-peak motion amplitudes of 10 or 20 mm ($10 \cdot \sin$, $20 \cdot \sin$, $10 \cdot \sin^4$ and $20 \cdot \sin^4$), and additionally with one curve following an irregular, patient-specific respiration pattern (Patient) with mean cycle period of 6.5 seconds

and mean internal motion amplitude of 14 mm. The shape of the internal motion trajectory differed slightly from the actual pressure input waveform due to hysteresis effects in the phantom [20].

Treatment planning

The phantom was operated with the five respiration patterns while phase-sorted four-dimensional computed-tomography (4D-CT) scans were taken with a SOMATOM Definition AS Open (Siemens AG, Germany) CT scanner. An average CT and ten breathing phases (phase CTs) were reconstructed using the RPM system (Varian Medical System, Palo Alto, CA). The gross tumor volumes (GTV) were delineated in all phase CTs. They were used to adapt the planning target volume (PTV) to match the five respiration patterns and the four investigated motion-management techniques:

- **ITV concept:** The entire tumor excursion, retrieved from the 4DCT, was contoured as internal target volume (ITV). A safety margin of 5 mm was added for the PTV_{ITV}.
- **MidV principle:** The mid-position of the tumors from the 4DCT phases was estimated. The phase with the tumor closest to this mid-position was estimated and taken as GTV_{MIDV}. The extent of tumor motion was retrieved from the 4DCT. Probabilistic margins based on the van-Herk formula [3] were added to the GTV_{MIDV} to get the PTV_{MIDV}. The margin recipe guaranteed that 90% of patients in the population receive a minimum cumulative GTV dose of at least 80% of the prescribed dose.
- **Gating:** The gating window with a 30% duty cycle was set at end of inhale to maximize the tumor-heart separation and increased lung volume during irradiation. The residual motion within this gating window was retrieved from the 4DCT data set and later used as gating threshold. The tumor volumes of the corresponding three phases were added to the GTV_{GATE}. A fixed 5-mm margin was added for the PTV_{GATE}.
- **Tracking:** GTV_{TRACK} was also chosen to be the tumor volume closest to the mid-position, but a fixed 5-mm margin was added for the PTV_{TRACK}.

Treatment plans for SBRT using volumetric modulated arc therapy were optimized with Eclipse, version 11.0.31 (Varian Medical System, Palo Alto, CA), and doses were calculated with the analytical anisotropic algorithm (AAA) on the average CT. A dose of 8x6 Gy was prescribed to the 65% isodose line around the PTV, allowing for high dose increase towards the central part. Lung, heart and spinal cord were contoured as organs at risk (OAR) and spared as much as possible in the optimization process. The spinal cord was constrained to a dose maximum below 32 Gy [21]. All treatment plans consisted of four co-planar, full arcs with an avoidance sector to spare the contralateral side of the lung.

Treatment delivery

Treatments were delivered to LuCa using a TrueBeam linear accelerator (Varian Medical System, Palo Alto, CA). A 3D cone-beam CT was taken and a 6D match was performed to position the tumor isocentrically. For gating and tracking treatments, Calypso transponders (Varian Medical System, Palo Alto, CA) were inserted into the tumor, monitoring its motion in real-time. The tracking system latency, which includes the time needed for position detection, signal processing and final repositioning of the couch, was reported for the same couch tracking system to be in the range of 187 to 246 ms for sine motion patterns with periods from 8 to 2 seconds, if no motion prediction algorithm is used [22]. To mitigate the influence of the system latency, a fast Kalman prediction filter was applied to the input signal and the predicted tumor position was used for the application of tracking treatments.

For the gating treatments, the residual motion measured in the phase-gating window at the planning stage was set as gating threshold. The Calypso signal triggered the irradiation only when the tumor position was within the threshold, prolonging the overall treatment time by a factor of 3.

For the tracking treatments, the predicted tumor motion was compensated with the PerfectPitch treatment couch using the iTools Tracking software (Varian Medical System, Palo Alto, CA). Figure 2 shows the control loop for gating and tracking treatment delivery.

In total, 24 treatments were measured, 20 for all combinations of respiration patterns and motion-management techniques, and additionally one static delivery for each technique. For each treatment, one fraction of 6 Gy was delivered and later scaled to a full treatment.

Film measurements

The dose was measured with Gafchromic EBT² films (Ashland Inc., USA) inside tumor. The tumor films were placed in coronal direction and neatly covered the size of the tumor (58 mm diameter) at the inserts with approximately 1 mm accuracy. Each measurement was performed once with one film per insert. The irradiated films were scanned twice with an Epson scanner (Seiko Epson Corporation, Japan). The two scans were averaged to correct for scanning noise. The green color channel of the film was converted to radiation dose in Matlab (The MathWorks Inc., USA) using a sheet specific five-step calibration set on the bottom of the sheet. A mean filter

over 6x6 pixels (1.02x1.02 mm²) was applied to the measured film data to adjust for noise. To correct for intra-sheet dose fluctuations, a homogeneously irradiated film sheet, irradiated with 7.6 Gy, was investigated. These fluctuations are caused by both film and scanner inhomogeneities. The homogeneously irradiated film was divided into 9 segments according to the tumor film positions on a film sheet. The mean dose in each segment was evaluated. Calibration factors were introduced to adjust the mean of each segment to 7.6 Gy. The inter-sheet uncertainty was estimated by using two additional homogeneously irradiated film sheets and comparing the mean values of the segments after applying the same calibration factors. Differences were measured to be $-0.4\% \pm 0.6\%$ (mean $\pm$ std). Intra-segment dose variations were not addressed with this method. They showed 1.4% (std) dose fluctuations over single segments.

Dosimetric comparisons

The four motion-management techniques were compared regarding tumor coverage and sparing of organs at risk with dose measurements and dose parameters from the treatment planning system. Dose was measured with film in the tumor and heart, and next to the spinal cord with a PinPoint ionization chamber (PTW-Freiburg GmbH, Germany).

Firstly, the dose distributions in the tumor were analyzed. The 2D dose planes from the planned 3D dose distribution were taken at the position of both film inserts. Corresponding regions were taken for evaluation from the irradiated films and the planned doses. A margin of 2 mm at the film edged was excluded from the evaluation due to dose uncertainties at the film fringes and to exclude marks on the film which were used for alignment. Near minimum (D_{99}), near maximum (D_1) and mean dose (D_{mean}) were retrieved and used for the calculation of homogeneity indices ($H_{2-98} = 100 \cdot (D_2 - D_{98}) / D_{mean}$). The changes in homogeneity ($\Delta H_{2-98} = H_{2-98, calc} - H_{2-98, meas}$) were reported. The areas of the films receiving more than the planned minimum dose ($A_{>D_{min}}$), and more than the prescribed 6 Gy ($A_{>6Gy}$) were calculated. Gamma agreement scores ($GI_{3\%/2mm}$ and $GI_{5\%/2mm}$) between the measured and the planned doses, with gamma criteria of 3%/2 mm and 5%/2 mm, were evaluated.

Secondly, the dosimetric comparison of OARs was performed. Planned OAR dose parameters, as mean heart dose, maximal spinal cord dose ($D_{0.5cc}$), mean lung dose (lung including tumor) and the lung volumes getting more than 5 or 20 Gy (V_{5Gy} and V_{20Gy} , respectively) were compared. For tracking, the intended shift of the phantom with the treatment couch was included in the planned OAR dose: The dose distribution of the tracking treatment plan was recalculated on each of the ten phase CTs, while the beam isocenter was shifted to the corresponding tumor isocenter. The summed-up dose was then displayed on the average CT.

Additionally, the mean heart doses from the film measurements and the measured PinPoint doses were compared.

Statistics

The values were grouped according to their technique and compared with a Kruskal-Wallis test. The significance level for inequality of the groups was set to a p -value of < 0.05 . The relations between motion amplitude and coverage parameters, and PTV size and organ doses were evaluated with Spearman rank correlations.

Results

Tumor coverage

Tumor dose parameters are summarized in Table 1. Median values over all respiration patterns are listed together with 25% and 75% quartiles and the static delivery. All measured mean doses (D_{mean}) were all within $\pm 3.2\%$ of the planned D_{mean} . Tracking and gating showed a tendency for higher measured than planned D_{mean} , while MidV and ITV showed mixed results.

All techniques covered the tumor with the prescribed dose ($A_{>6Gy} = 100\%$) and showed adequately large areas covered by at least the minimum planned dose ($A_{>D_{min}} > 99.0\%$) for all techniques, except for two measurements of the MidV principle (94.8% and 97.7%). Deviations in homogeneity indices ΔH_{2-98} were found to be higher for the ITV and the MidV principle (medians: 4.3 and 5.6 pp, respectively) than for gating and tracking (2.8 and 2.3 pp). However, the only parameter showing significance in the differences was ΔH_{2-98} ($p < 0.05$). No significant correlations of these parameters with motion amplitude or pattern were found.

Gamma agreement

The gamma agreement scores $GI_{3\%/2mm}$ and $GI_{5\%/2mm}$ are listed in Table 1 and corresponding gamma maps with over- and underdosed areas are shown in Figure 3. The $GI_{3\%/2mm}$ values for the ITV and the MidV principle (medians: 83.9% and 78.8%, respectively) were lower than for gating and tracking (90.2% and 88.2%), but without statistical significance. A significant negative correlation between the $GI_{3\%/2mm}$ values and motion amplitude was

found for the MidV (roh=-0.88, $p<0.05$) and tracking (roh=-0.88, $p<0.05$) cases, and between $GI_{5\%/2mm}$ and motion amplitude for MidV (roh=-0.97, $p<0.05$).

PTV reduction and OAR sparing

The PTV size, normalized to the tracking case, and the organ dose parameters are shown in Figure 4. The values correspond to a full treatment course (8x6 Gy=48 Gy) and are shown as boxplots, grouped according to the applied motion-management techniques.

A clear reduction of the target volume (PTV size) is visible from the ITV to the MidV principle, gating and tracking strategies. Similar reductions were found for organ dose parameters of the lung (lung D_{mean} , V_{20Gy} and V_{5Gy}), the spinal cord $D_{0.5cc}$ and the heart D_{mean} . Equality of the groups can be rejected with significance ($p<0.05$) for all OAR dose parameters. The reduction in OAR dose was significantly ($p<0.05$) correlated to the reduction in PTV size, as expected, with highest linear correlation coefficients for the lung D_{mean} , V_{20Gy} and V_{5Gy} (0.84, 0.73 and 0.95), spinal cord $D_{0.5cc}$ (0.77), and the planned and measured chamber dose (0.78 and 0.63). Lower correlation coefficients were found with the planned and measured heart D_{mean} (0.52 and 0.31), since it was only partially in the treatment fields.

Discussion

Patients with lung cancer and suboptimal respiration are at risk of acute and late radiation-induced toxicity. Motion-management techniques might thus allow decreasing the target volume and the radiation dose delivered to OARs, whilst delivering the full prescription dose to the target. This study investigated the dose delivery capability of the ITV concept, MidV principle, respiratory gating and dynamic couch tracking, and compared them in the lung phantom LuCa with regard to tumor coverage and organ dose sparing.

So far, performance studies on motion management have employed geometrical, rigid motion phantoms whose main advantage is motion reproducibility, neglecting human anatomy. Falk et al. [17] used a Delta⁴ phantom (ScandiDos, Sweden) mounted on a motion platform to measure delivery performance of gating and tracking strategies. Menten et al. [18] simply used films within solid water, mounted on a motion platform, to compare accuracy of different tracking strategies. The phantom employed for this study resembles human anatomy and allows for any desired tumor motion in the cranial-caudal direction. The phantom's components were chosen to have radiation-absorption properties equivalent human tissues. These anatomical features allowed using both OAR dose sparing and tumor coverage as endpoints.

Overall, the active motion-management techniques, gating and tracking, showed better dose sparing than the passive techniques, ITV and MidV concept. This benefit is mainly caused by the reduction of treatment volume, which is largest for tracking. The observed reductions are comparable to those of other authors. Depuydt et al. [8] reported a PTV reduction of 35% when changing from the ITV concept to a tracking scenario, and Guckenberger et al. [16] showed a comparable decrease in lung D_{mean} , changing from ITV over to a MidV or gating approach.

Although tracking allowed for the smallest PTV size, a benefit of gating over tracking was shown for heart D_{mean} and lung V_{20Gy} (Figure 4). For gating, the potential reduction in OAR dose is also influenced by the choice of the gating window at exhale or inhale, which affects the separation between PTV and OARs. In this work, a gating window at end of inhale was chosen. This yielded a bigger distance between the heart and the tumor, resulting in a sparing of the heart. Additionally, the dynamically changing isocenter was simulated for the tracking OAR dose. This results in a spread out of the target dose, and hence an increased lung V_{20Gy} .

It has to be mentioned, that the dose parameters of the lung were based on the lung volume including the tumor volume. The usual approach for reporting lung dose excluding the tumor volume would lead in this case to different lung volumes for each concept and motion trace and thereby bias the results. Additionally, the lung volume and shape of the phantom might not fully represent human beings. Consequently, the lung doses should rather be considered as an integral dose of the treatment and used as a relative evaluation between the techniques.

The location of the tumor in the phantom was limited to a fixed location and size. We expect that our conclusions for the tumor coverage are independent of the location similar for the lung dose, but probably for the spinal cord the dose values may change, based on the location of the tumor.

All techniques showed good tumor coverage ($A_{>Dmin}$) with slightly inferior results for the MidV technique. This was expected, since a minimum of 80% coverage in 90% of all cases was assumed in the margin calculation.

The lower pass rates ($GI_{3\%/2mm}$) and larger changes in homogeneity (ΔH_{2-98}) found for ITV and MidV principles could be explained by the interplay and the gradient effect. As opposed to the gating and tracking techniques, the tumor changes its relation to the beam isocenter in ITV and MidV treatment. This makes the passive techniques more sensitive to interplay and gradient effects. For the gating and tracking treatments, both effects

are negligible as long as the error in target localization and machine delay (detection and mitigation) are small. For larger system latencies, additional safety margins are required, which might reduce the benefit.

The tracking system used a Kalman prediction filter, which reduces the effects of the system latency, but errors in the prediction might still impact the results. The Kalman filter predicts the signal linearly from the current speed and direction of the target assuming continued motion. This might lead to overshoots. Additionally, the couch motion is limited by acceleration speed, and therefore might have problems mitigating steep motion gradients. Hansen et al. [22] reported RMSE for the use of a fast Kalman filter, as it was applied in this work. A reduction in RMSE from 2.45 mm down to 0.85 mm was observed for lung motion curves when couch tracking was applied.

This work focused on couch tracking as tumor tracking method. Other tracking systems are assumed to give similar benefits for tracking over other motion-management techniques. A multi-institutional study was performed by Colvill et al. [23] to compare real-time adaptive therapy with robotic, gimbaled, MLC and couch tracking. The four modalities were found to perform similarly on the 2%/2 mm and 3%/3 mm failure criteria.

The Calypso transponders were inserted directly in the moving tumor, resulting in an ideal surrogate-to-tumor relation. In the clinical setting for lung cancer treatments, the transponders are normally implanted close to the tumor, in an accessible airway which may not move completely in phase with the tumor. Therefore, the phantom measurements might represent insufficiently cases with uncertainty in the surrogate-to-tumor relationship. Alternatively, externally-located surrogates combined with a correlation model can be used for position estimation [24]. However, external surrogates also increase the positional uncertainty due to potential deviations from the internal-to-external correlation model [25].

A limitation of the LuCa phantom was the hysteresis between input pressure and actual tumor motion, due to which rapid accelerations of the tumor were possible [20]. Regarding the overall tracking latency of 200-300 ms, these steep motion gradients might not be properly compensated. The exponential sinusoids ($10 \cdot \sin^4$ and $20 \cdot \sin^4$) showed some tracking errors at these gradients. However, all tracking measurements showed good tumor coverage.

The Gafchromic films were placed in coronal planes at two different depths in the tumor. This coronal setup allowed capturing the motion effects in the pre-dominant cranial-caudal direction. However, the anterior and posterior edges of the tumor were not covered. But judging from the mainly longitudinal motion direction and rotational symmetry of the irradiation, it was assumed that those edges show similar behavior than the left and right edges, which were covered by the film.

Gafchromic films have good spatial resolution, but are prone to noise and film inhomogeneities. Mean filters and inhomogeneity corrections were applied during the light-transmission-to-dose conversion of the green channel. The residual intra- and inter-sheet uncertainty of film measurements was estimated to be below 3%. Using two films per insert would further reduce the uncertainties and noise, and should be considered for further measurements. The Calypso system and cone beam CTs allowed setting up the tumor within 1 mm translational and 1° rotational offset to the reference position. The dose comparisons were made between doses measured in the phantom and 2D dose planes exported from the treatment plan. Additional factors as dose-calculation and machine uncertainties also influence the accuracy of these comparisons. The phantom's lung tissue is of lower density than human lung tissue. This could be the reason that the dose estimated by the treatment planning system underestimated the GTV mean dose. The Calypso array further absorbs 1.5% to 2% of the radiation penetrating through it [26]. These effects together might explain the overall low $GI_{3\%/2mm}$ as it can be seen in the static deliveries which yielded $GI_{3\%/2mm}$ values around 92%.

The study was limited to simple and mostly periodic respiration patterns in the cranial-caudal direction, and only single fractions were investigated. Single fraction deliveries represent the worst case scenario. Further work has to be done looking at the fractionation effect as well as looking at more complex motion patterns or motion patterns changing over the course of treatment. To better distinguish the benefit of one motion-management technique to another, additional measurements should be performed with larger variety of motion amplitudes and respiratory periods. For real patients, other sources of error, such as baseline shifts and changes in the respiratory motion characteristics over a course of treatment, have to be considered. Investigations into the robustness of the techniques with respect to these changes would be of high interest, but it is expected that under these conditions, tracking and gating with internal position markers would perform better than ITV and MidV. However, tracking accuracy is also limited by tumor deformations [27] if they are not considered in the planning process. For simplicity, the present work was performed with a rigid tumor. Deformations of the tumor volume could be considered by using a deformable tumor material, but challenges of dosimetry within deforming tissue have to be addressed.

Conclusion

The passive motion-management techniques (ITV and MidV) mitigated the motion with detectable, but clinically insignificant dose inhomogeneities. However, the larger treatment volumes incurred a penalty in the dose to organs at risk relative to gating and tracking. Beam gating based on the Calypso system provided good results in the measured endpoints. However, in this case, the overall treatment time increased by a factor of 3. On the other hand, the dynamic couch tracking was able to achieve adequate tumor coverage when compared to other respiratory motion-management techniques and at the same time was able to reduce the organ doses comparable to gating strategies, while no prolongation of delivery time was required.

Conflict of interest

The authors have to state no conflicts of interest.

Acknowledgements

This work was supported by the grants 320030-1483942 and CR32I3_153491 of the Swiss National Science Foundation.

Figures

Figure 1: Average CT of LuCa with tumor, heart and Pinpoint: Transverse (A), coronal (B) and sagittal (C) plane.

Figure 2: Control loop: The detected tumor motion (radiofrequency signal) is sent to the computer, which controls i) the triggering of the beam for gating or ii) the counter motion with the treatment couch for tracking.

Figure 3: Gamma maps of the anterior (top) and posterior (bottom) tumor films with 3%/2 mm and 5%/2 mm pass criteria, compared to the planned dose. Regions failing the gamma criterion are marked in black (higher) and white (lower dose than planned).

Figure 4: PTV size, normalized to the tracking PTV (top left), and OAR dose parameters, shown as boxplots over the five respiration patterns, grouped according to the motion-management techniques (white: planned values, grey: measured values). Connections with grey brackets indicate groups with significantly different distributions (Kruskal-Wallis, $p < 0.05$).

Tables

Table 1: Evaluated parameters from film measurements inside the moving tumor, representing the accumulated tumor dose, compared to the planned dose.

	ITV concept	MidV	Gating	Tracking
ΔD_{mean} (Gy)	0.01 (-0.03-0.21) [0.20]	-0.04 (-0.11-0.16) [0.19]	0.09 (0.03-0.12) [-0.12]	0.16 (0.11-0.20) [0.09]
$A_{>D_{\text{min}}}$ (%)	99.8 (99.6-99.9) [99.5]	99.1 (97.0-99.5) [100]	99.9 (99.4-99.9) [99.0]	100 (99.9-100) [99.8]
ΔH_{2-98} (pp) °	3.3 (3.0-3.7) [4.2]	4.5 (2.9-5.8) [1.2]	2.4 (2.0-3.4) [0.8]	1.8 (0.6-2.0) [1.3]
$GS_{3\%/2\text{mm}}$ (%)	83.9 (75.4-90.0) [93.9]	78.8 (66.0-81.2) * [89.1]	90.2 (85.5-91.2) [92.1]	88.2 (86.9-91.6) * [93.7]
$GS_{5\%/2\text{mm}}$ (%)	93.1 (85.4-96.5) [98.2]	91.4 (81.0-92.1) * [98.3]	96.8 (96.0-97.3) [99.3]	96.5 (96.1-97.2) [97.8]

Values: Median (q_{25} - q_{75}), [static delivery], pp: percentage points,

*: correlated to motion amplitude, °: significantly different between techniques

Bibliography

- [1] S. C. Erridge, Y. Seppenwoolde, S. H. Muller, M. van Herk, K. De Jaeger, J. S. Belderbos, L. J. Boersma and J. V. Lebesque, "Portal imaging to assess set-up errors, tumor motion and tumor shrinkage during conformal radiotherapy of non-small cell lung cancer," *Radiotherapy and Oncology*, vol. 66, no. 1, pp. 75-85, 2003.
- [2] A. Wambersie and T. Landgerg, "ICRU Report 62: Prescribing, Recording and Reporting Photon Beam Therapy," *ICRU Publ Bethesda MD*, 1999.
- [3] M. van Herk, P. Remeijer, C. Rasch and J. V. Lebesque, "The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy," *International Journal of Radiation Oncology* Biology* Physics*, vol. 47, no. 4, pp. 1121-1135, 2000.
- [4] K. Ohara, T. Okumura, M. Akisada, T. Inada, T. Mori, H. Yokota and M. J. Calaguas, "Irradiation synchronized with respiration gate," *International Journal of Radiation Oncology* Biology* Physics*, vol. 17, no. 4, pp. 853-857, 1989.
- [5] P. Keall, V. Kini, S. Vedam and R. Mohan, "Potential radiotherapy improvements with respiratory gating," *Australasian Physics & Engineering Sciences in Medicine*, vol. 25, no. 1, pp. 1-6, 2002.
- [6] A. Schweikard, H. Shiomi and J. Adler, "Respiration tracking in radiosurgery," *Medical Physics*, vol. 31, no. 10, pp. 2738-2741, 2004.
- [7] K. Takayama, T. Mizowaki, M. Kokubo, N. Kawada, H. Nakayama, Y. Narita, K. Nagano, Y. Kamino and M. Hiraoka, "Initial validations for pursuing irradiation using a gimbals tracking system," *Radiotherapy and Oncology*, vol. 93, no. 1, pp. 45-49, 2009.
- [8] T. Depuydt, K. Poels, D. Verellen, B. Engels, C. Collen, M. Buleteanu, R. Van den Begin, M. Boussaer, M. Duchateau, T. Gevaert, G. Storme and M. De Ridder, "Treating patients with real-time tumor tracking using the Vero gimbaled linac system: implementation and first review," *Radiotherapy and Oncology*, vol. 112, no. 3, pp. 343-351, 2014.
- [9] P. Keall, V. Kini, S. Vedam and R. Mohan, "Motion adaptive x-ray therapy: a feasibility study," *Physics in Medicine and Biology*, vol. 46, no. 1, p. 1, 2001.
- [10] P. J. Keall, E. Colvill, R. O'Brien, J. A. Ng, P. R. Poulsen, T. Eade, A. Kneebone and J. T. Booth, "The first clinical implementation of electromagnetic transponder-guided MLC tracking," *Medical physics*, vol. 41, no. 2, p. 020702, 2014.
- [11] E. Colvill, J. T. Booth, R. O'Brien, T. N. Eade, A. B. Kneebone, P. R. Poulsen and P. J. Keall, "Multileaf collimator tracking improves dose delivery for prostate cancer radiation therapy:

- Results of the first clinical trial," *International Journal of Radiation Oncology*Biophysics*, vol. 92, no. 5, pp. 1141-1147, 2015.
- [12] D. D'Souza, S. A. Naqvi and X. Y. Cedric, "Real-time intra-fraction-motion tracking using the treatment couch: a feasibility study," *Physics in Medicine and Biology*, vol. 50, no. 17, p. 4021, 2005.
 - [13] S. Lang, J. Zeimet, G. Ochsner, M. S. Daners, O. Riesterer and S. Klöck, "Development and evaluation of a prototype tracking system using the treatment couch," *Medical physics*, vol. 41, no. 2, p. 021720, 2014.
 - [14] E. Chin, S. Loewen, A. Nichol and K. Otto, "4D VMAT, gated VMAT, and 3D VMAT for stereotactic body radiation therapy in lung," *Physics in medicine and biology*, vol. 58, no. 4, p. 749, 2013.
 - [15] E. Chin and K. Otto, "Investigation of a novel algorithm for true 4D-VMAT planning with comparison to tracked, gated and static delivery," *Medical physics*, vol. 38, no. 5, pp. 2698-2707, 2011.
 - [16] M. Guckenberger, A. Kavanagh, S. Webb and M. Brada, "A novel respiratory motion compensation strategy combining gated beam delivery," *Radiotherapy and Oncology*, vol. 98, no. 3, pp. 317-322, 2011.
 - [17] M. Falk, T. Pommer, P. Keall, S. Korreman, G. Persson, P. Poulsen and P. M. Rosenschöld, "Motion management during IMAT treatment of mobile lung tumors—A comparison of MLC tracking and gated delivery," *Medical physics*, vol. 41, no. 10, p. 101707, 2014.
 - [18] M. J. Menten, M. Guckenberger, C. Herrmann, A. Krauss, S. Nill, U. Oelfke and J. Wilbert, "Comparison of a multileaf collimator tracking system and a robotic treatment couch tracking system for organ motion compensation during radiotherapy," *Medical physics*, vol. 39, no. 11, pp. 7032-7041, 2012.
 - [19] K. Bernatowicz, A. J. Lomax and A. Knopf, "Comparative study of layered and volumetric rescanning for different scanning speeds of proton beam in liver patients," *Physics in medicine and biology*, vol. 58, no. 22, p. 7905, 2013.
 - [20] R. Perrin, M. Peroni, K. Bernatowicz, M. Zakova, A. Knopf, S. Safai, T. Parkel and A. Lomax, "A Realistic Breathing Phantom of the Thorax for Testing New Motion Mitigation Techniques with Scanning Proton Therapy," *AAPM 56th Annual Meeting*, pp. OC-0484, 2014.
 - [21] S. Adebahr, S. Collette, E. Shash, M. Lambrecht, C. Le Pechoux, C. Faivre-Finn, D. De Ruyscher, H. Peulen, J. Belderbos, R. Dziadziuszko, C. Fink, M. Guckenberger, C. Hurkmans and U. Nestle, "LungTech, an EORTC Phase II trial of stereotactic body radiotherapy for centrally located lung tumours: a clinical perspective," *The British journal of radiology*, vol. 88, no. 1051, p. 20150036, 2015.
 - [22] R. Hansen, T. Ravkilde, E. S. Worm, J. Toftegaard, C. Grau, K. Macek and P. R. Poulsen, "Electromagnetic guided couch and multileaf collimator tracking on a TrueBeam accelerator," *Medical physics*, vol. 43, no. 5, pp. 2387-98, 2016.
 - [23] E. Colvill, J. N. S. Booth, M. Fast, J. Bedford, U. Oelfke, M. Nakamura, P. Poulsen, E. Worm and R. Hansen, "A dosimetric comparison of real-time adaptive and non-adaptive radiotherapy: A multi-institutional study encompassing robotic, gimbaled, multileaf collimator and couch tracking," *Radiotherapy and Oncology*, vol. 119, no. 1, pp. 159-165, 2016.
 - [24] J. Hoisak, E. Katharina, R. Tirona, P. Cheung and J.-P. Pignol, "Prediction of lung tumour position based on spirometry and on abdominal displacement: Accuracy and reproducibility," *Radiotherapy and Oncology*, vol. 3, pp. 339-346, 2006.
 - [25] M. F. Spadea, M. Peroni, E. Preve, M. Riboldi, G. Baroni, G. T. Chen and G. C. Sharp, "Uncertainties in lung motion prediction relying on external surrogate: a 4DCT study in regular vs. irregular breathers," *Technology in cancer research & treatment*, vol. 9, no. 3, pp. 307-15, 2010.
 - [26] L. Santanam, C. Noel, T. R. Willoughby, J. Esthappan, S. Mutic, E. E. Klein, D. A. Low and P. J. Parikh, "Quality assurance for clinical implementation of an electromagnetic tracking system," *Medical physics*, vol. 36, no. 8, pp. 3477-3486, 2009.
 - [27] S. Senthil, M. Dahele, B. J. Slotman and S. Senan, "Investigating strategies to reduce toxicity in stereotactic ablative radiotherapy for central lung tumors," *Acta Oncologica*, vol. 53, no. 3, pp. 330-335, 2014.