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Original article

The long- and short-term variability of breathing induced tumor motion in lung and liver over the course of a radiotherapy treatment

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ABSTRACT

Purpose: To evaluate the short and long-term variability of breathing induced tumor motion.

Materials and methods: 3D tumor motion of 19 lung and 18 liver lesions captured over the course of an SBRT treatment were evaluated and compared to the motion on 4D-CT. An implanted fiducial could be used for unambiguous motion information. Fast orthogonal fluoroscopy (FF) sequences, included in the treatment workflow, were used to evaluate motion during treatment.

Materials and methods: Several motion parameters were compared between different FF sequences from the same fraction to evaluate the intrafraction variability. To assess interfraction variability, amplitude and hysteresis were compared between fractions and with the 3D tumor motion registered by 4D-CT. Population based margins, necessary on top of the ITV to capture all motion variability, were calculated based on the motion captured during treatment.

Results: Baseline drift in the cranio-caudal (CC) or anterior-poster (AP) direction is significant (ie. >5 mm) for a large group of patients, in contrary to intrafraction amplitude and hysteresis variability. However, a correlation between intrafraction amplitude variability and mean motion amplitude was found (Pearson's correlation coefficient, $r = 0.72$, $p < 10^{-4}$). Interfraction variability in amplitude is significant for 46% of all lesions. As such, 4D-CT accurately captures the motion during treatment for some fractions but not for all. Accounting for motion variability during treatment increases the PTV margins in all directions, most significantly in CC from 5 mm to 13.7 mm for lung and 8.0 mm for liver.

Conclusion: Both short-term and day-to-day tumor motion variability can be significant, especially for lesions moving with amplitudes above 7 mm. Abandoning passive motion management strategies in favor of more active ones is advised.

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Human breathing is a well-documented interplay between contracting and relaxing muscles, resulting in an increase in the volume of the chest cavity, which causes a decrease in pressure, allowing air to flow into the lungs [1]. All this causes periodic motion of the thoracic, abdominal and likely even the pelvic anatomy, in the order of centimeters and this over a timespan of several seconds [2,3]. During external radiotherapy of targets located in these regions, these temporal anatomic changes can be the cause of significant geometrical treatment errors, affecting tumor control and increasing the normal tissue complication probability [4,5]. With the increasing use of intensity modulated radiotherapy (IMRT), the introduction of proton and heavy ion therapy, and the idea of radiomics to target specific subtumoral regions, these errors become even more critical [6–8].

Over the past few years, significant time and resources have been allocated toward solving the respiratory-motion issue, resulting in an arsenal of motion management strategies, from dedicated treatment margins in the planning stage to real-time tumor tracking (RTTT) during dose delivery [9,9–15]. The aim of all strategies is to ensure sufficient dose to the target, while keeping the dose to surrounding healthy tissue as low as reasonably possible.

Often these objectives and constraints, but also the appropriate treatment modality, are evaluated using a pre-treatment four-dimensional computed tomography study (4D-CT) [16]. This imaging modality delivers information not only about the tumor motion, but also about the location of organs at risk (OAR) during

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different breathing phases. However, a regular 4D-CT takes less than one minute to acquire, encompassing a maximum of 15 breathing cycles. This means that a single 4D-CT does not contain any information concerning the day-to-day variability of the breathing induced tumor- and OAR motion.

These days, in-room imaging modalities are omnipresent and range from orthogonal kV imaging to cone-beam CT (CBCT) and EPID-imaging. However, due to low tumor contrast on X-ray images and a lack of markerless localization solutions, in-room target imaging is usually exclusively used for momentary positioning, while online respiratory-motion monitoring is generally left out [17,18]. As such, a considerable part of motion management relies on a single pre-treatment 4D-CT, a snapshot in time [19]. Does this suffice?

In this study, we analyzed the 3D tumor motion of highly moving lung and liver tumors over the entire course of treatment, and during 4D-CT, using an implanted fiducial as benchmark. As such, tumor motion, and more specifically intra- and interfraction variability, could be evaluated. In addition, it was investigated whether 4D-CT is a reliable source to represent the tumor motion during the entire course of treatment.

Materials and methods

Patients and treatment

Thirty-four patients, comprising thirty-seven lesions, treated with RTTT on the Vero SBRT system (BrainLAB AG, Feldkirchen, Germany) were included in this study. The group consisted of 9 primary lesions of non-small cell lung cancer patients (lesions 1–9, 4×12 Gy), 10 lung lesions of oligometastatic cancer patients (lesions 10–19, 10×5 Gy) and 18 liver lesions of oligometastatic cancer patients (lesions 20–37, 10×5 Gy) of which one patient had 2 (lesions 22–23) and another patient had 3 (lesions 29–31).

For each patient, 4–8 days prior to the pre-treatment planning 4D-CT, a single 0.75 mm thick Visicoil TM (IBA, Louvain-La-Neuve, Belgium), used as a fiducial, was percutaneously implanted in or within a centimeter of the tumor. The high-contrast fiducial is used to support automatic 3D localization of the tumor on kV images to build the hybrid correlation model for RTTT based on the external breathing signal, as well as to facilitate real-time treatment verification [20–21].

Data acquisition

A 4D-CT was acquired for all patients approximately one week before the first treatment fraction. A 4D multislice CT scanner (Somatom Definition AS; Siemens Medical Solutions, Erlangen, Germany) with 2 mm slice thickness and 0,98 mm in-plane image resolution was used for all 4D-CT studies. Amplitude-based reconstruction was carried out in 10 breathing phases using an infrared-based Real-time Position intrafraction Management system (Varian, Palo Alto, CA) and build-in Siemens reconstruction software [22].

During treatment, tumor motion was registered using '20 s fluoroscopy (11 Hz) sequences' using two orthogonal on-board kV imagers at ±45° from the MV beam. Resolution at isocenter was 0.3×0.3 mm^2. The sequences were acquired during free breathing and 3D target data extracted from the images was used to build a hybrid correlation model between the internal tumor motion and an external breathing signal. At least one sequence was acquired before each treatment fraction, while additional sequences were acquired throughout the treatment fraction if the correlation model had to be rebuild, ie. when the difference between the predicted and detected target position is larger than 3 mm. This was the case in 61% of all fractions. As such, intrafraction tumor motion variability and baseline drift could be evaluated.

Tumor motion evaluation

The center-of-mass (COM) of a single high-contrast fiducial implanted in or near the tumor was used as the tumor location in both 4D-CT and fluoroscopy sequences. All reconstructed 4D-CT studies were imported in MIM software (MIM software Inc., Cleveland, OH). The fiducial COM was localized manually in each breathing phase. To automatically detect the fiducial COM in each X-ray image of all fluoroscopy sequences, an in-house developed intensity-based template matching algorithm was applied. A verification study of this algorithm, based on a comparison with manual localization, found the accuracy to be within 1 mm. Each 2D coordinate pair of orthogonal X-rays was transformed to one 3D coordinate using machine-specific transformation matrices. As such, one to seven – depending on the number of correlation model rebuilds – 3D tumor motion trajectories of 20 s were available per fraction.

The peak-to-peak motion amplitude in 4D-CT was defined as the maximum distance between the COM of the fiducial in any two breathing phases, without making use of the surrogate signal. Between these phases, the motion amplitude was determined in the left–right (LR), anterior-posterior (AP) and cranial-caudal (CC) direction, separately. The predominant direction of motion was defined as the one with the highest amplitude. The peak-to-peak motion amplitude during treatment was calculated for each breathing cycle in the 3D motion trajectory, in each direction separately (LR, CC and AP). The average ± SD of all breathing cycles was calculated per fraction to verify the intrafraction variability (1 SD). Interfraction variability was assessed between average amplitudes per fraction, with the average interfraction amplitude variability defined as 1 SD of the average of all average amplitudes per fractions. Hysteresis, defined as the maximum distance between the inhalation and exhalation trajectory perpendicular to the predominant direction of motion [23], was extracted from each breathing cycle and averaged per fraction. The intrafraction variability was quantified using 1 SD. Baseline drift was also defined in three directions separately (LR, AP, CC), and defined as the distance between the average tumor position in consecutive fluoroscopy sequences acquired during the same fraction.

Margin evaluation

Both the intra- and interfraction tumor motion variabilities, as well as the accuracy of 4D-CT to represent the tumor motion, were translated to clinically relevant quantities by recalculating the PTV margin applied on ITV in our clinic. The previous PTV margin did not take into account motion variability and was equal to 5 mm in each direction. It was calculated for non-ITV lung patients based on the margin recipe of Van Herk (for 90% of all patients, the GTV receives at least 95% of the prescribed dose) and translated to ITV patients to ensure sufficient target coverage [24,25]. The PTV component for motion variability, necessary on top of the ITV, was calculated so that the GTV was covered 95% of the treatment time, or in this case in 95% of the fluoro sequences, see supplementary materials Fig. S1. The margins were calculated in two different scenarios. First, it was calculated without taking baseline drift into account, so assuming continuous baseline drift correction is performed during treatment. On the contrary, the second includes baseline drift as a variability. The PTV components were calculated for each lesion in three directions separately (LR, CC and AP) to evaluate the asymmetry of the tumor motion variability. In addition, based on the values for each lesion, population based PTV components were calculated so that for 90% of the population

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