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4DCT-based evaluation of lung tumor motion during the breathing cycle

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The aim of this study was to quantify the variability of pre-treatment lung tumor motion during a single breathing period for 55 non-small cell lung cancer (NSCLC) targets. The influence of breathing on the volume and position of lung tumor was examined by comparing the information about tumor from respiratory-correlated four-dimensional computed tomography (4DCT) and three-dimensional computed tomography (3DCT) obtained without respiratory monitoring. The impact of age, gender, lung volume changes and immobilization device on tumor respiratory motion was evaluated. Based on the performed analysis, the significant differences were found between tumor volumes on 3DCT and 4DCT, although the comparison of volumes between 4DCT bins showed no statistically significant dependency. The significant differences between tumor center of mass coordinates in the cranial-caudal (CC) and anterior-posterior (AP) directions were found. According to the results of statistical testing, there was no impact of gender and immobilization device on detected tumor respiratory motion. The impact was found for patient's age, lung volume changes, tumor volume and its location in different lung segments. The dominant lung cancer motion was observed for smaller tumors (up to 20 cc) located in posterior, caudal segments. This effect was also associated with a large variation in the lung volume during one respiratory cycle, observed for older patients. The important finding of the study is connected with the description of different patterns of tumor motion in AP and CC directions.

Key words: lung, four-dimensional computed tomography, moving targets, respiratory motion, non-small cell lung cancer

For tumors significantly affected by respiratory motion (e.g. lung cancer), the quality of standard three-dimensional computed tomography (3DCT) images may be biased by motion artifacts that influence the size, shape and density of scanned anatomical structures (including the tumor) [1–8]. This degrades a precise determination of tumor dimension and its position and, finally, does not guarantee a safe, accurate and effective external beam dose delivery [9–11]. Thus, respiration is considered not only a major target motion cause, but also one of the biggest uncertainties, which may occur during the whole treatment course and affect not only the target located in the lung but also neighboring organs at risk (OARs) [12–15]. To manage this problem, several solutions applied to the CT scanning procedure were proposed, including CT scanning with very long scan times per slice (slow CT), CT in breath hold or forced shallow breathing and four-dimensional computed tomography (4DCT) [5, 16, 17]. The first three options have many limitations. First of all, the reliability of slow CT is limited to peripheral tumors, whereas breath hold and forced shallow prolong the treatment time. It is not acceptable due to medical condition (compromised pulmonary function) of some lung cancer patients, which excludes the use of breath hold or forced shallow breathing for free breathing in many cases [18]. Hence, in all those clinical situations, respiratory correlated 4DCT images are required to quantify the individual tumor and organ movements [19]. Precisely, during the 4DCT reconstruction, the respiratory signals are incorporated with the spatial three-dimensional CT image acquisition [12]. This enables to reconstruct the multiple CT series at defined phases of the breathing cycle [4, 6, 7] and to prepare the tumor contours on each reconstructed phase [5]. The summed contours represent the tumor motion envelope, which is defined as the internal target volume (ITV) [1, 16, 20]. Thus, ITV contains the tumor with an anisotropic margin that takes into account the physiological movement caused by the breathing process [5, 21]. Therefore, ITV could cover the tumor changes during the whole breathing cycle (in this case radiation is delivered during free breathing). On the

other hand, 4DCT information on individual respiratory motion characteristics allows to determine the time interval in which the patient will be exposed to radiation [5]. In this case, ITV is reconstructed only for the selected part of the complete breathing cycle and, consequently, the emission of ionizing radiation is controlled by a sensor system that maps the patient's breathing phase [5].

Taking into account the whole external beam radiation delivery, initially, the acquired 4DCT images could be used to evaluate the magnitude of target variations in the three dimensions [12], which is crucial in the case of large tumor motion. At this stage, it is still possible to introduce some modifications in anatomical fixation accessories in order to optimize dose delivered to the target and neighboring organs at risk [22]. From this point of view, 4DCT is a relatively simple procedure that enables the classification of tumors into subgroups, such as almost non-mobile or mobile ones. Such an attempt was made by Tan et al. [3], who correlated tumor motion characteristics with tumor- and patient-related factors, like location in an anatomical lobe and pulmonary zone, tumor volume, T-stage, smoking status or obstructive lung disease determined by spirometry. According to this publication, lung tumor location in lower lobes and lower pulmonary zones are the most significant predictors of cranial-caudal (CC) respiratory-induced motion. At first glance, the smoking status had a significant impact on respiratory-induced tumor motion in the anterior-posterior (AP) and cranial-caudal directions. Unfortunately, the differences found between smokers, ex-smokers and non-smokers groups were inconsistent analyzing the tumor movement in two previously mentioned directions. Probably, it was due to the uncertainty related to overlapping factors as ex-smokers has proportionally more tumors located in lower lobes compared with non-smokers and smokers. Finally, tumor volume, T-stage and spirometry cannot be considered as factors determining lung tumor motion.

To complete analysis of Tan et al., the main goal of this work was to perform a broad analysis of 4DCT reconstructions. First of all, 4DCT data bins were used to quantify the variability in pre-treatment tumor motion during a single breathing period for patients with lung cancer. The influence of breathing on the volume and position of lung tumor was examined by comparing the information about tumor from 4DCT and 3DCT data (obtained with and without respiratory monitoring, respectively). As a next step, we aimed to evaluate the impact of age, gender, immobilization device and lung volume changes on tumor respiratory motion. Consequently, various lung tumor motion patterns were identified and later classified as a function of tumor location, its volume and other factors that proved to be relevant. Due to the fact that multiple patient and treatment related factors were taken into account for relatively large patients' population, this comprehensive motion analysis adds valuable knowledge to other motion studies published in this field so far.

Patients and methods

Patient characteristics. Fifty-five non-small cell lung cancer (NSCLC) targets were retrospectively analyzed. No additional selection criteria were used. At the time of treatment patients (20 women and 35 men) ranged in age from 31 to 89 years (40 patients were ≥60 years of age). Thirty-five right-sided and 20 left-sided tumors were assessed.

Immobilization and CT scanning procedure. Patients were positioned supine with knee support and with the arms placed above the head on an adjustable arm support (25 patients) or with hands along the body on the vacuum mattress (30 patients). Prior to scanning, to achieve a regular and stable breathing pattern, the verbal coaching was performed with the main instruction to breath normally and lightly [12, 23, 24]. Patients were scanned after a reproducible pattern of respiration was observed. The imaging procedure consisted of free-breathing 3DCT and respiratory-correlated CT (4DCT) and was performed on Somatom Sensation Open CT scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with an external marker-based solution, Real-Time Position Management (RPM) Respiratory Gating System (Varian Medical Systems, Palo Alto, CA, USA) [24]. Eleven phases equally distributed over the breathing cycle were reconstructed for each 4DCT study according to a breathing signal that was acquired using the detector (a small block with reflective markers) that was placed on the patient's thorax [24–26]. The infrared video camera recorded the displacement of the block to continuously detect the breathing cycle throughout the cine scan. Finally, each reconstructed image was assigned to a specific respiratory phase (called "bin"). All CT series were acquired with a slice thickness of 2 mm [25].

Delineation procedure. CT series were transferred to Eclipse v.10.0 Treatment Planning System (Varian Medical Systems, Palo Alto, CA, USA). The tumor (GTV – gross tumor volume or CTV – clinical target volume, due to the inability to perform a GTV delineation) was manually contoured by a single experienced clinician both on 3DCT slices acquired for the planning purpose, as well as on all 4DCT bins. The single senior radiation therapist was responsible for reviewing all contours [1, 25]. Then, the internal target volume (ITV) was reconstructed as the union of the targets at all breathing phases, taking into account the possibilities of the tumor variation in position, shape and size [6, 27]. The 4DCT tumor mean volume (4DCT mean) with standard deviation (4DCT SD) for all phases within one breathing cycle was calculated. To describe the contouring variation, the mean coefficient of variation defined as a standard deviation from 4DCT tumor mean volume divided by 4DCT tumor mean volume (4DCT SD/4DCT mean) was used. Out of all 55 4DCT data sets, for 42 it was possible to delineate the whole volume of both lungs. For the other patients, it was not possible due to the lack of entire lung volume on the available 4DCT scans. This delineation process was performed automatically. The contoured

lung volumes (without trachea inclusion) were analyzed to achieve the lung mean coefficient of variation (calculated as a standard deviation from 4DCT lung mean volume divided by 4DCT lung mean volume). This parameter was chosen to detect lung volumes changes and described them as estimated spirometry results.

Respiratory motion analysis. First, the tumor respiratory motion was detected by analyzing its center of mass (COM) delineated on each 4DCT bins. The impact of COM changes was estimated by describing its position using the left-right (LR), cranial-caudal (CC) and anterior-posterior (AP) coordinates. Maximum normal inspiration (CT0) was the first reconstructed 4DCT phase. It was chosen to be the reference one, thus the COM coordinates from other 4DCT phases (CT10–CT100) were compared to CT0.

Initially, the excursion distance (ED) in each direction was calculated as the absolute distance between COM coordinates on maximum normal inspiration (CT0) and maximum normal expiration (CT50) [28].

According to literature findings, lung tumor may move changing both its shape and size in an anisotropic manner. That is why, additionally, the range of tumor motion called peak to peak motion (PtP) was obtained by subtracting the minimum coordinate from the maximum coordinate value [21]. Consequently, peak to peak motion is the parameter that is not directly dependent from specific breathing phases (like maximum normal inspiration or maximum normal expiration). For example, for a single patient, a peak to peak motion could be calculated as the difference between maximum normal inspiration (CT0) and CT60, whereas excursion distance was always determined between maximum normal inspiration (CT0) and maximum normal expiration (CT50). Finally, peak to peak motion (PtP) was compared with the excursion distance (ED).

Statistical analysis. The dependence between detected tumor respiratory motion and:

(i) patient gender,
(ii) patient age,
(iii) immobilization device,
(iv) tumor volume,
(v) tumor location
    a. left vs. right lung;
    b. cranial vs. cranial-middle vs. middle vs. middle-caudal vs. caudal lung segments,
    c. anterior vs. anterior-middle vs. middle vs. middle-posterior vs. posterior location,
(iv) lung volume changes (pseudo spirometry results described by mean lung coefficient of variation),

were verified. Statistical analysis was performed using the XLSTAT software version 2018.6 (Addinsoft. XLSTAT statistical and data analysis solution, Boston, USA) with a p-value below 0.05 deemed to be statistically significant. Based on non-normality of the samples (according to the Shapiro Wilk test), the Wilcoxon and Friedman tests were used to compare the delineated tumor volumes, the differences in their COM coordinates, the lung mean coefficient of variation and the dependence between parameters defining tumor motion (PtP and ED). For the Friedman test (when more than 2 paired samples were compared) the post-hoc testing using the Nemenyi method were selected. The influence of gender, age and immobilization device used on tumor motion was verified using Mann-Whitney and Kruskal-Wallis tests. For more than 2 unpaired samples compared with Kruskal-Wallis test, the Dunn testing operation with Bonferroni correction was performed to ascertain, which sample set was responsible for detected global differences.

Results

Tumor volume and the analysis of its variation. The mean tumor volume from 3DCT was 22.09 cc (range 0.32–107.32 cc), whereas the mean tumor volume from 4DCT was 23.71 cc (range 0.21–113.36 cc). According to the results of statistical analysis, significant differences were found between tumor volumes on 3DCT and 4DCT (Wilcoxon's $p=0.034$), although the comparison of tumor volumes between 4DCT bins showed no statistically significant differences (Friedman's $p=0.564$). The standard deviation of the mean tumor volume delineated between single 4DCT bins equaled 1.79 cc (range 0.03–9.14 cc). The mean coefficient of variation, the parameter which combines the mean tumor volume and its standard deviation, equaled 9.43% (range 1.98–49.25%). In one case, the mean coefficient of variation reached 49.25%, which indicated an extremely high contouring variation. The number of observations for coefficient variation higher than 10, 15 and 20% equaled 17, 5 and 3, respectively.

After adding the breathing motion component, the delineated mean ITV volume from 4DCT for all patients was 35.61 cc (range 0.54–153.24 cc). ITV from 4DCT was recognized as the structure with significantly bigger volume than the tumor volume on 3DCT (Wilcoxon's $p<0.0001$). The volume statistics calculated after analyzing the delineated tumor for the whole analyzed 3DCT data sets and one exemplary, randomly selected patient (patient no. 30) are summarized in Table 1.

Tumor motion based on COM analysis. Statistical verification of the differences between tumor COM coordinates on subsequent 4DCT phases showed the existence of significant differences between them in the CC and AP directions (Friedman's $p<0.0001$). The post-hoc analysis (with Nemenyi's procedure) verified that in the CC direction the differences were insignificant only for subsequent 4DCT bins. In the AP direction, the differences were revealed between the first and second half of the full respiratory cycle (between phases associated with inspiration and expiration). The differences were insignificant in the LR direction (Friedman's $p=0.988$). Analyzing tumor center of mass (COM) changes relative to reference COM coordinates from CT0, the highest center of mass (COM) movements were calculated in the CC direction (Table 2). Therefore, for this axis the whole

Table 1. Summary of tumor descriptive statistics results calculated for the subsequent 4DCT bins (CT0–CT100) on the cohort of our study group and randomly selected patient no 30. Additionally, the tumor volumes averaged over all 4DCT bins (V_{avg}(4DCT)) with standard deviations (V_{SD}(4DCT)), mean tumor coefficient of variation (V_{SD}/V_{avg}), tumor volumes delineated on planning CT (V(3DCT)) and detected ITV volumes (ITV(4DCT)) were presented.

Descriptive statistics	Tumor Volumes [cc] at subsequent 4DCT bins											V_{avg}(4DCT) [cc]	V_{SD}(4DCT) [cc]	V_{SD}/V_{avg} [%]	V(3DCT) [cc]	ITV(4DCT) [cc]
	CT0	CT10	CT20	CT30	CT40	CT50	CT60	CT70	CT80	CT90	CT100					
Mean	24.2	24.4	23.6	23.4	23.7	23.8	23.9	23.3	23.4	23.6	23.7	23.7	1.8	9.4	22.1	35.6
Max	121.3	112.8	108.6	112.1	116.8	119.4	119.1	118.7	118.4	118.0	119.4	113.4	9.1	49.3	107.3	153.2
Min	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.2	0.2	0.3	0.2	0.2	0.0	2.0	0.3	0.5
Patient no. 30	44.4	48.7	50.9	53.6	53.9	53.2	52.5	50.4	51.4	50.9	45.1	50.5	3.2	6.4	45.2	57.4

Table 2. Tumor center of mass (COM) changes relative to the reference 4DCT bin (CT0). COM coordinates presented in three directions.

Descriptive Statistics	CT0–CT10	CT0–CT20	CT0–CT30	CT0–CT40	CT0–CT50	CT0–CT60	CT0–CT70	CT0–CT80	CT0–CT90	CT0–CT100
LEFT-RIGHT DIRECTION										
Mean [cm]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
SD [cm]	0.1	0.1	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1
Min [cm]	−0.2	−0.4	−0.5	−0.6	−0.6	−0.5	−0.3	−0.3	−0.3	−0.3
Max [cm]	0.3	0.5	0.5	0.5	0.6	0.4	0.4	0.3	0.3	0.2
Median [cm]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
CRANIAL-CAUDAL DIRECTION										
Mean [cm]	−0.2	−0.3	−0.4	−0.5	−0.5	−0.5	−0.3	−0.1	0.0	0.0
SD [cm]	0.2	0.4	0.5	0.6	0.6	0.6	0.5	0.3	0.2	0.2
Min [cm]	−0.6	−1.8	−2.3	−2.2	−2.3	−2.5	−2.5	−1.1	−0.9	−0.4
Max [cm]	0.2	0.3	0.3	0.5	0.5	0.4	0.4	0.7	0.7	0.7
Median [cm]	−0.1	−0.2	−0.2	−0.3	−0.3	−0.2	−0.2	−0.1	0.0	0.0
ANTERIOR-POSTERIOR DIRECTION										
Mean [cm]	−0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.0	0.0
SD [cm]	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.2	0.2	0.2
Min [cm]	−1.3	−1.4	−1.4	−1.3	−1.3	−1.4	−1.2	−1.3	−1.4	−1.3
Max [cm]	0.3	0.5	0.6	0.7	0.6	0.8	0.7	0.6	0.3	0.2
Median [cm]	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.0	0.0

lungs were divided into 5 segments: cranial, cranial-middle, middle, middle-caudal and caudal. The COM coordinates changes detected for tumors located in the above-mentioned segments, with association with 4DCT subsequent bins, are presented in Figures 1A–E. It shows that tumor location in the middle-caudal and caudal segments are burdened with the highest tumor COM coordinates changes throughout one respiratory cycle.

Excursion distance vs. peak to peak displacement. For each direction, the dependence between excursion distance (ED) and peak to peak (PtP) displacement was verified. The statistically significant differences in the LR, CC and AP directions were found (Wilcoxon's $p<0.0001$).

According to the analysis results from the previous section, the highest center of mass (COM) movements were calculated in the CC direction. Also, the highest values of ED and PtP parameters were detected for this axis (Table 3). That is why, the whole lungs were divided again into 5 segments (cranial, cranial-middle, middle, middle-caudal and caudal) along the CC direction. The changes of ED and PtP averaged vectors for tumors located in the above-mentioned segments of the left and right lungs are presented in Figure 2. It also shows the absolute difference between those vectors calculated for selected lung segments. The above-described comparative analysis between ED and PtP displacement led to the conclusion that further analysis should be performed using PtP motion as the parameter indicating respiratory motion.

The PtP shift detected for each analyzed tumor and averaged over the whole study group was 0.22 cm, 0.64 cm, 0.30 cm in the LR, CC and AP direction, respectively. The gathered and analyzed data showed that PtP motion in the CC direction was predominant. The highest detected relative PtP shift reached 2.61 cm in this direction (Table 3). In almost half of the patients from the analyzed group, the 0.5 cm PtP displacement in the CC direction was found, whereas in two other directions such tumor displacement was detected for 3 patients (in LR) and 6 patients (in AP).

Ten patients had tumor PtP displacement of >1 cm in the CC direction, whereof in the case of 6 patients, the displacement was >1.5 cm. For 2 patients with extreme breathing motion in this direction, the 2.01 cm and 2.61 cm COM shift was found.

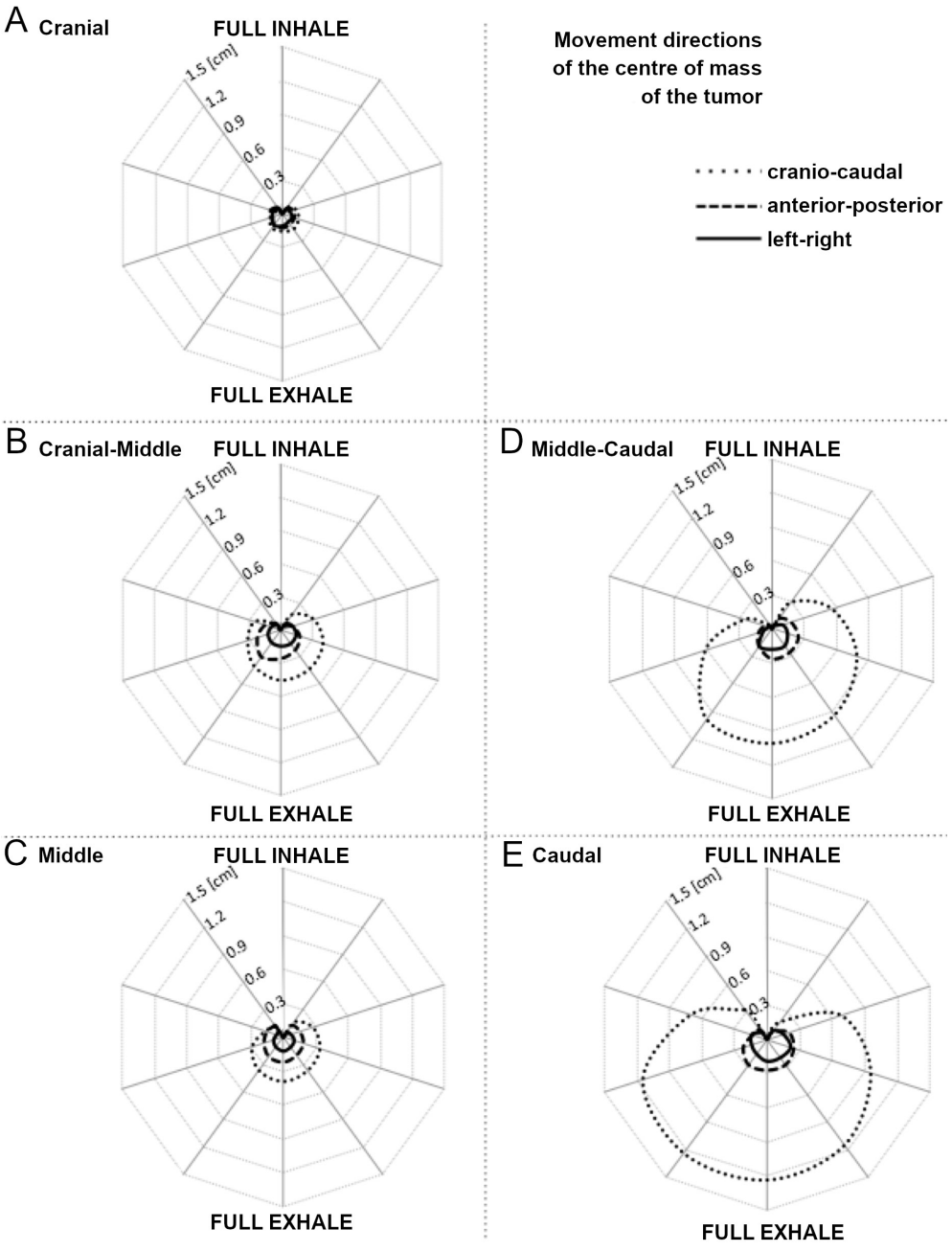

Figure 1. The center of mass (COM) coordinates changes over one respiratory cycle, detected for tumors located in lung segments determined along the CC axis (A–E).

Peak to peak analysis versus patient-related factors. Gender was the first analyzed patient-related factor, which according to statistical testing, had no impact on PtP motion of the tumor (Mann-Whitney p=0.146, p=0.069 and p=0.105 for LR, CC and AP directions, respectively). In Table 4, the lung 4DCT characteristics averaged over 42 patients was presented with the mean lung volume calculated over all 4DCT bins, its standard deviation and lung mean coefficient of variation.

In contrast to gender, age and mean lung coefficient of variation turned out to be parameters that statistically significantly affected the PtP values (Wilcoxon's $p<0.0001$ in all directions).

As the patients were immobilized on a vacuum mattress or with adjustable arm support, the influence of immobilization device used on PtP motion was also verified. According to Mann-Whitney test, there was no statistical difference

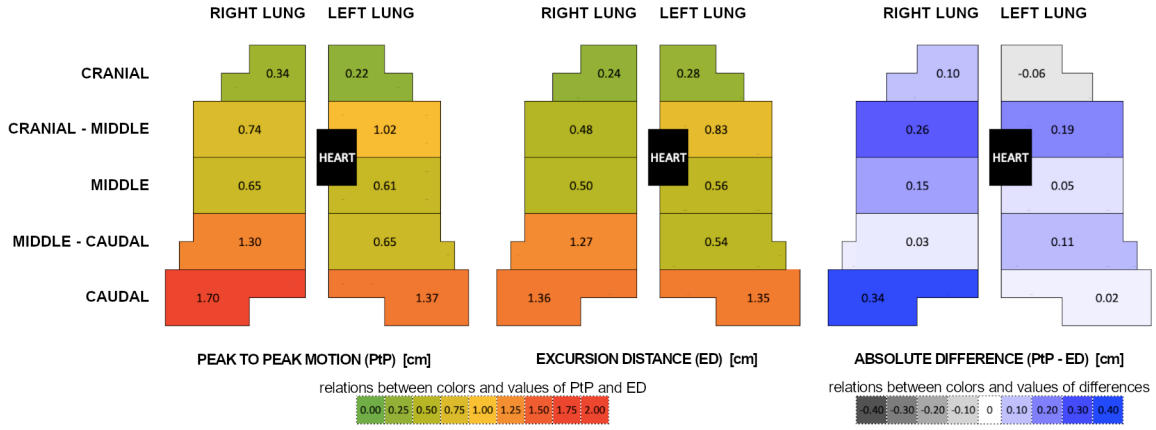

Figure 2. The changes of excursion distance (ED) and peak to peak (PtP) averaged vectors taking into account the location of the tumor in the left or right lung and one of the segments along the CC axis. The absolute differences between those vectors (PtP-ED) were also presented.

between using a vacuum mattress and adjustable arm support (Mann-Whitney p=0.660, p=0.679 and p=0.318 in LR, CC and AP axes, respectively).

Peak to peak analysis versus tumor volume and its location. No matter which volume was taken into account (the mean tumor volume calculated over all 4DCT bins or ITV volume from 4DCT), the statistically significant differences were found between them and PtP motion in every direction (all Wilcoxon's p<0.0001). Analyzing tumor location, in the first step, all tumors were divided in those located in the left lung and those located in right one. Tumor position in the left versus right lung was found to have no influence on detected PtP motion (Mann-Whitney p=0.130, p=0.958 and p=0.306 in LR, CC and AP directions, respectively).

Then, all tumors were classified into particular segments:

(i) cranial, cranial-middle, middle, middle-caudal or caudal segments,

(ii) and anterior, anterior-middle, middle, middle-posterior and posterior segments.

The location in one of the described segments had no impact on PtP movement in the AP and LR directions. The impact of location was significant in the CC axis (Kruskal-Wallis' p=0.003 for the first specified segments (i) and p=0.005 for the second (ii) group of segments). The post-hoc analysis (Dunn with Bonferroni correction) revealed that the differences between cranial and caudal, anterior and posterior as well as middle and posterior tumor locations were responsible for the differences.

Table 3. Summary of descriptive statistics results for excursion distance (ED) and peak to peak (PtP) displacement on the cohort of our study group.

Descriptive Statistics	Left-Right		Cranial-Caudal		Anterior-Posterior	
	PtP	ED	PtP	ED	PtP	ED
Mean [cm]	0.22	0.14	0.64	0.51	0.30	0.23
SD [cm]	0.15	0.14	0.59	0.56	0.17	0.21
Min [cm]	0.03	0.00	0.04	0.02	0.03	0.00
Max [cm]	0.69	0.60	2.61	2.32	0.81	1.32
Median [cm]	0.18	0.09	0.45	0.28	0.27	0.19

Discussion

Analysis of tumor volume variation. The accurate definition of tumor volume is crucial for high-precision external beam delivery regardless of cancer location. For tumors located in the lung, additional information of tumor and organ motion during one respiratory cycle is necessary to perform conscious and precise external beam radiation therapy treatment. For the purpose of this study, lung cancer patients with 4DCT imaging were retrospectively analyzed.

Table 4. Summary of lung descriptive statistics results calculated for the subsequent 4DCT bins (CT0–CT100) on the cohort of our study group and patient no 30. Additionally, the lung volumes averaged over all 4DCT bins (V_{avg}(4DCT)) with standard deviations (V_{SD}(4DCT)) and lung mean coefficient of variation (V_{SD}/V_{avg}) were presented.

Descriptive statistics	Lung Volumes [cc] at subsequent 4DCT bins											V_{avg}(4DCT) [cc]	V_{SD}(4DCT) [cc]	V_{SD}/V_{avg} [%]
	CT0	CT10	CT20	CT30	CT40	CT50	CT60	CT70	CT80	CT90	CT100			
Mean [cc]	3901.7	3738.4	3579.8	3471.8	3404.7	3362.5	3367.8	3472.4	3665.3	3862.0	3901.3	3611.6	209.2	6.2
Max [cc]	7791.3	7627.8	7519.0	7437.5	7362.7	7282.5	7276.8	7420.1	7581.9	7759.8	7787.5	7529.4	531.7	12.1
Min [cc]	1917.6	1744.5	1572.5	1514.3	1457.2	1393.3	1378.7	1468.5	1680.1	1868.2	1917.3	1628.4	73.1	1.9
Patient no. 30	2510.3	2291.2	2076.0	1952.5	1883.9	1841.6	1849.3	1993.2	2271.0	2499.9	2510.1	2152.6	259.7	12.1

Although the information about motion may be obtained by monitoring patient's respiration (independent of 4DCT availability), accurate prediction of volume and tumor dimension deformation is not possible without respiratory signals incorporated with the spatial 3DCT as performed using 4DCT [6, 12]. Analyzing our results, the essential information is that tumor volume differences between subsequent 4DCT bins did not vary significantly. However, the reconstructed ITV occurred to be significantly larger than the tumor volume delineated on planning 3DCT. This demonstrated that in most cases within our study group, the tumor position changes with its deformation are the main causes of significant increase of the lung target volume over one respiratory cycle. Finally, considerable volume differences and substantial variations of tumor relative position were detected when comparing single 3DCT simulation with the 4DCT reconstructions. The same tendency was reported by Lin et al. [12]. Their analysis revealed that 4DCT-based tumor volume was significantly larger than 3DCT-based tumor size among 17 NSCLC patients enrolled in their study. It should be emphasized that the Lin et al. patient group was characterized not only by a smaller number, but also by larger tumor volumes (mean 3DCT tumor volume: 51.36 cc) than those from our study group (mean 3DCT tumor volume: 22.09 cc). In the following part, Lin et al. analyzed the dose distribution for the moving lung targets. In reference to this study, there are countless articles in which the different factors were analyzed as significant or insignificant predictors of mean tumor position variation. In most cases, such analysis is performed as a part of external beam radiotherapy intrafraction motion analysis. Our aim was to prepare a complex analysis based on a big group of consecutive patients with the emphasis on defining the 4DCT-based respiratory motion of verbally coached patients. Then, the dependence between detected tumor respiratory motion and patient- or treatment-related factors was verified. From this point of view, the presented analysis is a complement to the article published by Tan et al. [3], which correlated tumor motion characteristics with various patient-related factors. The above-mentioned publication is restricted to the tumor volume analysis performed only on the maximum respiration phase, which was then considered a reference value for tumor volume. To complement this previous analysis, we decided to perform tumor volume measurements on every 4DCT bin, reconstruct it into ITV and compare with tumor volume contoured on planning 3DCT, which was discussed above. Additionally, we used center of mass (COM) data to estimate tumor motion using two parameters (peak to peak and excursion distance) whereas Tan et al. tracked tumor movements only based on changes in GTV COM coordinates.

The presented single 4DCT-based methodology always raises some concern about regularity and reproducibility of respiratory motion during treatment delivery, as one of the assumptions of our analysis is that 4DCT breathing cycle is stable and typical (meaning representative) for each patient from the study group [8, 13]. Our patients were verbally coached how to breathe and the scanning procedure was performed only when the reproducible pattern of respiration was observed. From our perspective, any breathing training method is indispensable to eliminate significant cycle-to-cycle variations, as such fluctuations were very often noticed at the beginning of motion monitoring (during breathing training).

Thus, authors are convinced that at the contouring stage the good quality of the CT images reconstruction for each patient was assured. In the further step, to provide the confidence of tumor reproducibility and precision of the whole treatment, during all ITV-based external beam radiation delivery, the accuracy of tumor motion envelope from a single 4DCT procedure should be verified with pre-treatment image guidance (e.g. using fiducials or cone beam CT, CBCT) [8, 13, 14, 20, 29].

Tumor motion based on COM analysis. Verifying the discrepancies between the tumor center of mass (COM) coordinates on the subsequent 4DCT bins, for the CC and AP axes significant differences were found. Further analysis revealed completely different patterns (mechanisms) of tumor motion in these directions: for AP the differences were detected between the first and second half of the full imaged respiratory period giving a clear picture that the significant differences occurred between the inspiration and expiration part of the respiratory cycle. A completely different dependence was verified in the CC direction where COM coordinates only for subsequent 4DCT bins (e.g. coordinates on CT0 and CT10, CT10 and CT20 etc.) showed no significant difference. Between the coordinates for the remaining 4DCT bins, the differences were found (e.g. between coordinates on CT0 and CT20, CT0 and CT30 etc.) and there was no implication of the inspiration or expiration part of the respiratory cycle on it. These results were correlated with the diaphragm motion (as it is the most important inhalation muscle). Its contraction increases the chest cavity dimension, especially in the CC direction, which has also strong implication, when taking into account the dependence between lung tumors motion and its location [3]. As graphically presented in Figure 1A, the movement of tumor COM throughout one respiratory cycle was comparable in the CC, AP and LR directions for tumors located in the cranial segments. The significance of LR and AP COM shifts increased towards the caudal segments, but for each analyzed group of segments it did not exceed 3 mm. Globally, this trend was preserved also for CC shifts, with the need to underline that for the middle-caudal and caudal segments the tumor movement throughout one respiratory cycle was significant (exceeding 1 cm). Insightful analysis revealed a statistically insignificant but graphically visible trend of a slightly bigger COM movement for tumors located in the cranial-middle segments as compared to the middle segments. At first, it was quite surprising but visual inspection of cranial-middle tumors demonstrated that for

some patients' tumor location was close to the mediastinum. It is not clear if such tumor location directly affects increased mobility. There are some studies, like the one published by Mercieca et al. [26], in which the tumor interobserver delineation variability was associated with its vicinity to the mediastinum. This might suggest that the variability of tumor delineation on each 4DCT bin tends to be more prone to slightly larger variations than those demonstrated in the case of other tumors locations. Following this path, a similar problem could be detected for tumors located in more than one region [26], which also complicates the delineation process. To minimize such potential delineation variability, at first step, all contours were manually performed by a single experienced physician. Then, according to the ESTRO ACROP guidelines [25], a single senior radiation therapist was responsible for discussing, reviewing and rearranging (if needed) all contours.

Peak to peak versus patient related factors. The dependence between detected tumor respiratory motion (described by a parameter called peak to peak, PtP) and patient-related factors showed that gender as well as the position of the tumor in the left or right lung are not significantly influencing the tumor motion. Nor was there any difference found among patients immobilized supine with the arms positioned above the head on an adjustable arm support and patients laid on the vacuum mattress with hands along the body. According to EORTC recommendations [30], patients should be positioned with arms above the head to enable more beam positions. This valuable consideration has been given with the remark that in the case of individual patients this immobilization requirement cannot be achieved. On the contrary, the ESTRO ACROP guidelines refers to the optional use of more sophisticated immobilization systems, such as stereotactic body frame, BodyFix approach or abdominal compression [20]. In Shah et al. [28] publication, in which intrafraction variation of mean tumor position was assessed during CBCT-guided stereotactic lung treatment, patients were positioned using: stereotactic body frame (Elekta Oncology Systems, Stockholm, Sweden), custom alpha cradle (KGF Enterprises, Chesterfield, MI), BodyFix (Elekta Oncology Systems, Stockholm, Sweden) or a hybrid customized set-up system combining the alpha cradle and BodyFix vacuum suction. In that study, significant differences were found between the above-mentioned immobilization devices and intrafraction variation of mean target position. Compared to other three immobilization devices, a stereotactic frame significantly reduced daily treatments with intrafraction tumor variation greater than 2 mm. The two different set-up systems (supine position with the arms placed above the head and hands along the body on the vacuum mattress) used among our patients, did not influence significantly the values of PtP displacements. That is why, authors are convinced that if the detailed instructions and enough time are given to reach patients' comfort, even simple immobilization device can lead to achieve patients' stability.

During Shah et al. [28] intrafraction variation analysis, GTV size in the mediolateral and anterior-posterior dimension, as well as age and gender, were not found to be significant predictors of 2 mm mean target position variation. This is in contrary to our results, according to which the age had an influence on the PtP displacement (with increasing age, the detected respiratory motion increased). The difference might be related to the fact that in Shah et al. study selection of an immobilizing device was associated with the age of the patient (e.g. frame patients were significantly older than patients immobilized alternatively). Among patients from our study group, there was no such a trend as patients were positioned depending on treatment method, i.e. on CyberKnife (vacuum mattress, hands along the body) or on a conventional linear accelerator (adjustable arm support).

Apart from the age, volume also proved to be a dominant factor affecting PtP motion. In this case, the tendency was noticed that the smallest tumors and those with ITV volume not exceeding 20 cc were characterized by higher values of PtP motion in every direction. Whereas in the AP and LR directions for those tumors the PtP motion reached 0.81 cm and 0.61 cm, respectively, and up to 1.99 cm in the CC axis. Although in the AP the maximum PtP value (0.81 cm) was detected for the tumors with ITV volumes of 15 cc and 19.39 cc, in the LR and CC direction the higher PtP values (of 0.69 cm and 2.61 cm) were revealed for tumors volumes of 153.24 cc (the biggest ITV in the whole study group) and 116.08 cc, respectively. This made us aware that statistical significance revealed between lung tumor motion and its volume showed the tendency, which have to be verified in clinical practice. This statistical dependence is in contrast to the results published by Tan et al. [3], as it did not report statistically significant influence of tumor volume on detected lung target breathing motion. In order to explain these mutually exclusive observations, it should be underlined that this study excluded patients with T4 stage and comorbid diseases which compromise respiration. For T1–T3 stage tumors Tan et al. reported that the tumor stage was insignificant predictor of respiratory-induced tumor motion in any direction. However, when defining patients' inclusion criteria for our study, tumor stage was not specified. Consequently, all tumor stages were included in the analysis (e.g. lung tumors causing bronchial obstruction), which could have an impact on the detected discrepancy.

Finally, the significant influence of the tumor location on PtP motion was detected in the AP and CC directions. Precisely, a statistical increase of this parameter was found for the caudal and posterior segments.

During data analysis, when creating a model of possible lung tumor motion, some additional factors (not appearing in the assumptions of the study) were observed and verified in literature. These were associated with rarely described, but very important aspect of more precise tumor location definition, which categorized all tumors into those suspended in lung tissues and attached to rigid structures

(e.g. peripheral tumor location or peripheral tumor location with broad chest wall contact) [9, 20]. Finally, respiratory motion does not only affect tumor volume, but also normal tissues around it. That is why, for the external beam radiotherapy purposes, for selected patients the organs at risk movement should be factored when irradiating the target located proximally to these structures [13] or planning at risk volume (PRV) should be created to check the tolerance dose for the expanded OAR [9].

References

[1] CAILLET V, KEALL PJ, COLVILL E, HARDCASTLE N, O'BRIEN R et al. MLC tracking for lung SABR reduces planning target volumes and dose to organs at risk. Radiother Oncol 2017; 124: 18–24. https://doi.org/10.1016/j.radonc.2017.06.016

[2] CHEN B, HU Y, LIU J, CAO AN, YE LX et al. Respiratory motion of adrenal gland metastases: Analyses using four-dimensional computed tomography images. Phys Med 2017; 38: 54–58. https://doi.org/10.1016/j.ejmp.2017.05.045

[3] TAN KV, THOMAS R, HARDCASTLE N, PHAM D, KRON T et al. Predictors of respiratory-induced lung tumor motion measured on four-dimensional computed tomography. Clin Oncol 2015; 27: 197–204. https://doi.org/10.1016/j.clon.2014.12.001

[4] GUCKENBERGER M, WILBERT J, MEYER J, BAIER K, RICHTER A et al. Is a single respiratory correlated 4D-CT study sufficient for evaluation of breathing motion? Int J Radiat Oncol Biol Phys 2007; 67: 1352–1359. https://doi.org/10.1016/j.ijrobp.2006.11.025

[5] ADAMCZYK M, PIOTROWSKI T. Respiratory motion and its compensation possibilities in the modern external beam radiotherapy of lung cancer. Nowotwory 2017; 67: 292–296.

[6] RODRIGUEZ-ROMERO R, CASTRO-TEJERO P. The influence of respiratory motion on CT image volume definition. Med Phys 2014; 41: 041701. https://doi.org/10.1118/1.4866889

[7] ZHUANG L, YAN D, LIANG J, IONASCU D, MANGONA V et al. Evaluation of image guided motion management methods in lung cancer radiotherapy. Med Phys 2014; 41: 031911. https://doi.org/10.1118/1.4866220

[8] DUNN L, KENNY J. A software platform for statistical evaluation of patient respiratory patterns in radiation therapy. Phys Med 2017; 42: 135–140. https://doi.org/10.1016/j.ejmp.2017.09.128

[9] SCHWARZ M, CATTANEO GM, MARRAZZO L. Geometrical and dosimetrical uncertainties in hypofractionated radiotherapy of the lung: A review. Phys Med 2017; 36: 126–139. https://doi.org/10.1016/j.ejmp.2017.02.011

[10] ADAMCZYK M, ADAMCZYK S, PIOTROWSKI T. Modelling the effects of lung cancer motion due to respiration. Nukleonika 2018; 63: 95–103.

[11] KNOPF A, NILL S, YOHANNES I, GRAEFF C, DOWDELL S et al. Challenges of radiotherapy: Report on the 4D treatment planning workshop 2013. Phys Med 2014; 30: 809–815. https://doi.org/10.1016/j.ejmp.2014.07.341

[12] LIN H, LU H, SHU L, HUANG H, CHEN H et al. Dosimetric study of a respiratory gating technique based on four-dimensional computed tomography in non-small-cell lung cancer. J Radiat Res 2014; 55: 583–588. https://doi.org/10.1093/jrr/rrt145

[13] ZOU W, YIN L, SHEN J, CORRADETTI MN, KIRK M et al. Dynamic simulation of motion effects in IMAT lung SBRT. Radiat Oncol 2014; 9: 225. https://doi.org/10.1186/s13014-014-0225-3

[14] MACIA I, GARAU M. Radiobiology of stereotactic body radiation therapy (SBRT). Rep Pract Oncol Radiother 2017; 22: 86–95. https://doi.org/10.1016/j.rpor.2017.02.010

[15] HARADA K, KATOH N, SUZUKI R, ITO YM, SHIMIZU S et al. Evaluation of the motion of lung tumors during stereotactic body radiation therapy (SBRT) with four-dimensional computed tomography (4DCT) using real-time tumor-tracking radiotherapy system (RTRT). Phys Med 2016; 32: 305–311. https://doi.org/10.1016/j.ejmp.2015.10.093

[16] MIURA H, OZAWA S, HAYATA M, TSUDA S, YAMADA K et al. Effect of tumor amplitude and frequency on 4D modeling of Vero4DRT system. Rep Pract Oncol Radiother 2017; 22: 290–294. https://doi.org/10.1016/j.rpor.2017.02.012

[17] AZNAR MC, WARREN S, HOOGEMAN M, JOSIPOVIC M. The impact of technology on the changing practice of lung SBRT. Phys Med 2018; 47: 129–138. https://doi.org/10.1016/j.ejmp.2017.12.020

[18] PEULEN H, BELDERBOS J, ROSSI M, SONKE JJ. Mid-ventilation based PTV margins in Stereotactic Body Radiotherapy (SBRT): a clinical evaluation. Radiother Oncol 2014; 110: 511–516. https://doi.org/10.1016/j.radonc.2014.01.010

[19] EHRHARDT J, WERNER R, SARING D, FRENZEL T, LU W et al. An optical flow based method for improved reconstruction of 4D CT data sets acquired during free breathing. Med Phys 2007; 34: 711–721. https://doi.org/10.1118/1.2431245

[20] GUCKENBERGER M, ANDRATSCHKE N, DIECKMANN K, HOOGEMAN MS, HOYER M et al. ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer. Radiother Oncol 2017; 124: 11–17. https://doi.org/10.1016/j.radonc.2017.05.012

[21] EHRBAR S, JOHL A, TARTAS A, STARK LS, RIESTERER O et al. ITV, mid-ventilation, gating or couch tracking - A comparison of respiratory motion-management techniques based on 4D dose calculation. Radiother Oncol 2017; 124: 80–88. https://doi.org/10.1016/j.radonc.2017.05.016

[22] MUTAF YD, ANTOLAK JA, BRINKMANN DH. The impact of temporal inaccuracies on 4DCT image quality. Med Phys 2007; 35: 1615–1622. https://doi.org/10.1118/1.2717404

[23] PEGURET N, DAHELE M, CUIJPERS JP, SLOTMAN BJ, VERBAKEL WF. Frameless high dose rate stereotactic lung radiotherapy: Intrafraction tumor position and delivery time. Radiother Oncol 2013; 107: 419–422. https://doi.org/10.1016/j.radonc.2013.04.019

[24] STERPIN E, JANSSENS G, ORDAN DE XIVRY J, GOOSSENS S, WANET M et al. Helical tomotherapy for SIB and hypo-fractionated treatments in lung carcinomas: A 4D Monte Carlo treatment planning study. Radiother Oncol 2012; 104: 173–180. https://doi.org/10.1016/j.radonc.2012.06.005

[25] NESTLE U, DE RUYSSCHER D, RICARDI U, GEETS X, BELDERBOS J et al. ESTRO ACROP guidelines for target volume definition in the treatment of locally advanced non-small cell lung cancer. Radiother Oncol 2018; 127: 1–5. https://doi.org/10.1016/j.radonc.2018.02.023

[26] MERCIECA S, BELDERBOS JSA, DE JAEGER K, SCHINAGL DAX, VAN DER VOORT VAN ZIJP N et al. Interobserver variability in the delineation of the primary lung cancer and lymph nodes on different four-dimensional computed tomography reconstructions. Radiother Oncol 2018; 126: 325–332. https://doi.org/10.1016/j.radonc.2017.11.020

[27] SERPA M, BAIER K, CREMERS F, GUCKENBERGER M, MEYER J. Suitability of markerless EPID tracking for tumor position verification in gated radiotherapy. Med Phys 2014; 41: 031702. https://doi.org/10.1118/1.4863597

[28] SHAH C, GRILLS IS, KESTIN LL, MCGRATH S, YE H et al. Intrafraction variation of mean tumor poition during image-guided hypofractionated stereotactic body radiotherapy for lung cancer. Int J Radiat Oncol Biol Phys 2012; 82: 1636–1641. https://doi.org/10.1016/j.ijrobp.2011.02.011

[29] CHANG JY. Intensity-modulated radiotherapy, not 3D conformal, is the preferred technique for treating locally advanced lung cancer. Semin Radiat Oncol 2015; 25: 110–116. https://doi.org/10.1016/j.semradonc.2014.11.002

[30] DE RUYSSCHER D, FAIVRE-FINN C, MOELLER D, NESTLE U, HURKMANS CW et al. Lung Group and the Radiation Oncology Group of the European Organization for Research and Treatment of Cancer (EORTC). European Organization for Research and Treatment of Cancer (EORTC) recommendations for planning and delivery of high-dose, high precision radiotherapy for lung cancer. Radiother Oncol 2017; 124: 1–10. https://doi.org/10.1016/j.radonc.2017.06.003