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REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY

ISSN: 1507-1367

e-ISSN: 2083-4640

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DOI: 10.5603/RPOR.a2022.0047

Article type: Research paper

Published online: 2022-04-07

Characteristics and dosimetric impact of intrafraction motion during peripheral lung cancer stereotactic radiotherapy: is a second midpoint cone beam computed tomography of added value?

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Abstract

Background: In our department, during lung stereotactic body radiation therapy (SBRT), all patients receive an intra-fractional midpoint cone beam computed tomography (CBCT). This study aimed to quantify the benefit of adding a second midpoint CBCT over a course of peripheral lung SBRT.

Materials and methods: Six-hundred-sixty-four CBCTs from 166 patients were retrospectively analyzed. Treatments were based on the internal target volume (ITV)

approach. An isotropic 0.5 cm margin was used to create the planning target volume (PTV) around the ITV. The prescribed dose was 48 Gy in 4 fractions to the PTV. Patients were divided into two groups: patients for whom the 3D-intra-fractional-variation (IFV) was < 0.5 cm (105 patients) and patients with at least one 3D-IFV ≥ 0.5 cm (high-risk groups). Plans simulating the dosimetric impact of the IFV were created as follows: the original 2 arcs (ARC) were copied into a new plan consisting of 4 times ARC1 and 4 times ARC2. The delivery of ARC1 was always assumed to have occurred with the isocenter initially coordinated, whereas the positions of ARC2 were modified for each arc by the measured the 3D-IFV.

Results: For the PTV, we obtained: D99% (Gy) = 45.2 vs. 48.2 Gy ($p < .0001$); Dmean = 53 vs. 54 Gy ($p < .0001$) for the reconstructed vs. planned dose values, respectively. For the ITV, the changes are less pronounced: D99%(Gy) = 52.2 vs. 53.6 Gy ($p = .0007$); Dmean = 56 vs. 56.8 Gy ($p = .0144$). The V48Gy(%)-ITV coverage did not statistically change between the delivered vs. planned dose ($p = .1803$). Regarding the organs at risk for both groups, dose-volume-histograms were near-identical.

Conclusion: We demonstrated that a single CBCT is sufficient and reliable to manage the IFV during peripheral lung SBRT.

Key words: IGRT; SBRT; intra-fraction motion

Introduction

Stereotactic body radiation therapy (SBRT) is an external beam radiation therapy method used to deliver a high dose in a few fractions with a short overall treatment time to extracranial sites of disease [1–4]. The efficacy of lung SBRT has been well demonstrated, but accurate planning and delivery presents a unique challenge [2]. Respiratory motion is a complex patient specific mechanism that has been found as the largest source of uncertainty within and between fractions [3, 5, 6]. In this context, the correlation among the target and the surrogate (i.e., external markers, bony anatomy) needs to be checked during the SBRT delivery [2]. However, this motion is insufficiently reproducible, no general patterns could be presumed

prior to planning or treatment [1–4, 6–8]. Failure to account for it could contribute to underdosing the target volume and/or overdosing the organs at risk (OARs) [1, 5, 9, 10].

The absence of motion management can sorely degrade the quality of any type of external-beam radiotherapy [11]. The most used techniques to quantify and integrate the respiratory motion are abdominal compression, breath-holding, forced shallow breathing, gating or tumor tracking [2, 4, 5, 7]. Four dimensions computed tomography (4DCT) is strongly recommended to gain accurate information about tumor movements and also to reduce systematic errors [2, 8, 9, 12].

Due to the high doses delivered in few fractions with small fields to anwell-defined target volume, the impact of inaccuracies is more significant [1]. To account for tumor motion the ICRU-reports-62, defined the internal target volume (ITV) [13]. Additionally, to reduce daily variations, image-guided-radiation-therapy (IGRT) has been developed to provide real-time information [1, 5].

To account for the inter-fraction (period between fractions) motion, IGRT is recommended, and daily online imaging is mandatory [2–6]. In such a way, systematic and random errors can be corrected prior to treatment [1]. In lung cancer radiotherapy cone beam computed tomography (CBCT) is the gold standard for IGRT [5]. Intra-fraction (during fraction) motion management consists of two real-time tasks: determination of target position and repositioning/modulation of the beam according to the estimated target position. Tumor motion in the lungs has been widely described [2, 3, 8, 10, 11]. Most of these studies are often with a small number of patients and heterogeneous (prescriptions and treatments). For lung tumors, direct tumor visualization or implanted fiducials are suitable options for alignment [1]. However, the latter are not always inserted exactly into the tumor and, thus, not always representative of the internal motion [15]. Moreover, in 10% to 23%, the trans-thoracic fiducial implantation leads to a pneumothorax [16].

For radiation therapy, it is crucial to contain the intra-fraction variation (IFV) effect throughout the course of SBRT. During such treatment, patient position should be monitored with available tools such as repeated imaging [4]. In this context, CBCT can be a powerful tool for assessing tumor motion [3]. CBCT has an acquisition time ≥ 60 seconds (over ≥ 15 breathing cycles) and for this reason can capture the average tumor position, which should correspond to the planning of 4D-CT [4]. Indeed, in lung SBRT the target is not stationary, contributing to a time-dependent density and distribution [2]. Moreover, 4D-CBCT has been widely developed and provides more accurate tumour localization. However, the acquisition

is usually longer than a classical 3D-CBCT and, therefore, will increase the time on treatment couch.

During a treatment fraction, time also plays a critical role, despite the immobilization device patients tend to drift away from their initial position [1, 9, 11, 12, 17–19]. Moreover, complex plans require longer beam-on times, and that can increase the chance of IFV [18, 20].

In our department, as a standard procedure during lung SBRT, all patients (regardless of tumour location) receive an additional midpoint CBCT, allowing us to make a further step in accuracy, assessing uncertainties and adjusting the beam delivery accordingly to the IFV. This study aims to: (1) quantify and characterize the IFV during a course of peripheral lung SBRT using an additional midpoint intra fraction CBCT and (2) incorporate the observed IFV into the treatment planning to simulate the potential dosimetric impact (a posteriori robust evaluation). Although it is to be expected that each IFV exceeding the planning target volume (PTV) margins could lead to potential discrepancies between planned and delivered ITV doses, a dosimetric simulation will help us quantify the actual impact on the ITV dose coverage. The extent of IFV impact is critical to understand and further explore possibilities for optimizing lung SBRT. This knowledge could allow improving and standardizing IGRT protocols and reducing the treatment field margins.

Materials and methods

Patients and design of study

For a cohort of 166 free-breathing lung SBRT patients for peripheral lesions treated with 4 fractions of 12 Gy, between 2014 and 2019, a number of treatment components (664 fractions) were retrospectively analyzed to investigate the intra-fraction displacements. An additional midpoint CBCT acquisition between the deliveries of the two volumetric modulated arc therapy (VMAT) provided quantitative data on IFV. Apart from an analysis of the IFV values themselves, the measured geometric uncertainties also allow us to determine the dosimetric impact of the IFV on the ITV coverage. The time required by each of the treatment delivery components was also measured.

Treatment planning

All patients were positioned in a supine position with arms above the head (MacroMedics ThoraxSupport™) with an adjustable arm and knee support. To provide immobilization during

subsequent planning and treatment a thoracic thermoplastic mold with four fasteners was made. Patients underwent quiet uncoached free-breathing slow CT-scan (GE CT RT 16 Large Bore, 2.5 mm slice thickness) and a 4D-CT image set (including 10 different 3DCT-scan) using the Real-time Position Management (RPM®, Varian Medical Systems, Palo Alto, CA, USA), placed on the patient's abdomen.

An ITV encompassing geometric uncertainties was delineated using a Maximum Intensity Projection (MIP) image and Average Intensity projection (AIP), both of them created from the 4D-CT image set, with additional corrections based on visual control on the 10 reconstructed breathing phases. No clinical target volume margins were used. An isotropic margin of 5 mm around the ITV was used to create the planning target volume (PTV). The organs at risk (OARs) were delineated according to the RTOG trial 0915 (NCCTGN0927).

Whereas the slow free-breathing CT was used for planning purposes for the early patients in this study, later patients were planned on the AIP CT. The prescription dose to PTV was 48 Gy in 4 fractions with a correction for tissue density. This is defined to be the 80% isodose line, 100% corresponded to the maximum dose delivered (within the PTV). Adequate target coverage was achieved when 95% of the PTV was covered by the assigned total dose and when 99% of the PTV received 90%. The volume outside the PTV receiving a dose > 105% (of the prescription dose) had to be 15% of the PTV, the target conformality was 1.2. Dose conformality and gradient quality were adjusted according to the parameters provided in TableS1 (RTOG trial 0915 Appendix). Treatment planning gave priority to the organs at risk OARs. Indeed, treatment plans had to meet contoured organ dose constraints as specified in TableS2 (RTOG trial 0915 Appendix). Patients were treated with volumetric modulated arc therapy including two ARCs (ARC_1 and ARC_2) using flattened beams (< 1000 Monitor-Units/min) and the analytic anisotropic algorithm (AAA) calculation within the Eclipse treatment planning (Varian Medical Systems, Palo Alto, CA, USA). We aim to treat successive fractions with 48 hours intervals.

Treatment delivery

Patients were initially set up to the CT reference position using lines on the thermoplastic immobilization device, aligned to the treatment room lasers. Patient positioning was then refined for each fraction by means of a CBCT (CBCT_1). Initial auto-matching based on the bone structures (clipbox to thoracic wall and/or vertebrae) was performed. Secondly, in order

to make sure that the lesion was well included within the ITV outline, a manual match was executed. Following the initial positioning, the first treatment beam (ARC1) was delivered. To assess the IFV, a second midpoint CBCT (CBCT_2), was performed prior to the delivery of the second beam (ARC_2). The online co-registrations were always performed by a radiation oncologist specialized in the lung SBRT. After the second CBCT, couch adjustments were made according to the online co-registration. For CBCT_2, the median and the 25^{th} 75^{th} percentile range [Q1;Q3] of the displacements were calculated in the left-right (LR), superior-inferior (SI) and anterior-posterior (AP) directions. The CBCT_2 IFV 3D vector δ was calculated as $\sqrt{(LR^2 + SI^2 + AP^2)}$. Moreover, we analyzed the time required per part during this treatment workflow: 1) initial patient positioning, CBCT_1 acquisition, CBCT_1 matching and positional adjustment, 2) ARC_1 delivery, 3) CBCT_2 acquisition and CBCT_2 matching and positional adjustment and 3) ARC_2 delivery. We also assessed the overall treatment time (OTT), i.e. the total number of days it took to complete all 4 treatment sessions.

Treatment dose reconstruction

Regardless of the location of the lesion, some intrafraction movement is to be expected on top of the positional setup uncertainties. This is traditionally taken into account by selecting the appropriate PTV margins to ensure ITV (or CTV) coverage at all times.

Although analysis of the IFV lies at the basis of this study, the IFV in itself does not suffice to draw any clear conclusions on the dosimetric impact of these geometric imprecisions. To determine the dosimetric impact of the IFV, the treatment planning system was used to simulate the a posteriori dosimetric dose distribution that would have occurred had we not re-assessed and corrected the patient positioning between subsequent treatment field deliveries. To do so, a new treatment plan was created as follows: the original arcs were copied into a new plan consisting of 4 times ARC1 and 4 times ARC2 (Fig. 1). The delivery of ARC1 was always assumed to have occurred with the isocenter coordinates as those in the original plan, whereas the positions of ARC2 were modified for each arc by the measured LR, SI, and AP displacement for that fraction. The MUs of the original delivery were maintained. The dose distribution, thus calculated, approximates the dose that would have been delivered had no CBCT_2 repositioning occurred. As it provides the total dose that would have accumulated

over all arcs and all treatment sessions, it allows DVHs analysis as well as a full visual inspection of the isodoses.

Patients were divided into two groups: patients for whom the 3D IFV was below 0.5 cm were considered low-risk regarding the dosimetric impact, whereas patients with at least one 3D IFV ≥ 0.5 cm were considered part of the high-risk group.

When using static treatment fields, patients for whom the IFV is below 0.5 cm should in theory be expected to maintain appropriate dosimetric ITV coverage, regardless of the intrafraction movement. When using VMAT treatment techniques, such a conclusion can no longer be drawn a priori as the VMAT optimization accounts for the inhomogeneities represented within the planning CT. We therefore also simulated a posteriori dosimetric dose distributions for patients for whom the 3D IFV was below 0.5 cm for all fractions.

The group for which the impact of the IFV movement was expected to be the largest consists, of course, of the patients with at least one 3D IFV ≥ 0.5 cm. For all patients in this group, the total dose distribution they would have received had the second midpoint CBCT not corrected for the IFV was simulated.

All reconstructed dose distributions were submitted to an individual investigation of the DVHs, hereby primarily focusing on the ITV coverage and on the OARs. The differences between planned and reconstructed dose in the high-risk group were submitted to statistical analysis using a Mann-Whitney test. Statistical analysis was performed using SPSS v 25.0 (Chicago, IL, USA) and GraphPad Prism v 7.00.

Results

Intrafraction motion

Within the cohort of 166 cases, 55% of the lesions were located in the upper lobe, 11% in the middle lobe and 34% in the lower lobe. Compared to the upper lobe lesions, lower and middle lesions showed a larger δ IFV (0.20 *vs.* 0.28 cm; p = .0006). For 105 patients (63.3%) the IFV never exceeded 0.5 cm. Treatment fractions for which the IFV exceeded 0.5 cm were distributed as follows: 40 patients (24.1%) had one such fraction; 14 (8.4%) had 2 fractions; 5 (3%) had 3 fractions and 2 patients (1.2%) had all 4 fractions with an δ IFV ≥ 0.5 cm (Fig. 3). In this group (n = 61), the median and the 25^{th} 75^{th} percentile range [Q1;Q3] ITV volume was

5.35 [3.2;10.3] cm^3. A box-and-whiskers Tukey plot representation of CBCT_2 displacements (X;Y;Z and δ 3D vector) for the 61 patients with at least one IFV ≥ 0.5 cm is given in Figure 4.

Dosimetric impact of the intrafraction motion

Treatment dose reconstructions made on a selection of patients from the low-risk IFV group show that good coverage of the ITV would have been obtained in all cases, even if no intra-fraction patient positioning had been performed: 100% of the ITV was always covered by the prescribed 48 Gy isodose [V48 (Gy)].

Treatment dose reconstructions on the high-risk patients also showed reassuring dose coverage for nearly all patients. Two dosimetric parameters were analyzed: V48 Gy (%) and the dose covering 99% of the volume, D99% (Gy). Although the delivered coverage of the PTV is inevitably inferior to the planned coverage because of the intrafraction motion, adequate ITV coverage is still assured in almost all cases (162/166), even if the second CBCT would not have been performed. Regarding the OARs (Dmax, Dmean, Dmin): for both the low- and high-risk IFV groups, DVHs of planned and reconstructed dose distributions were near-identical (no significant difference, nor even clinical relevance). Median [Q1–Q3] dose to the treated lung was : 60.1 Gy [59.1–61.1] *vs.* 60 Gy [59.89–60.2] for the reconstructed *vs.* planned dose values, respectively. No significant differences were observed for the Dmin ($p = .8056$), Dmean ($p = .04141$) or Dmax ($p = .4045$). In the same way for the heart, 8.8 Gy [0.7–19.9] *vs.* 9.1 Gy [0.8–19.8], also no statistically significant difference between Dmin ($p = .8694$), Dmean ($p = .9740$) or Dmax ($p = .4045$). The same observations were made for the spinal cord: 5.5 Gy [3.5–7.9] *vs.* 5.6 Gy [3.5-8.1], for the reconstructed *vs.* planned dose values, respectively, Dmin ($p = .7864$), Dmean ($p = .8417$) or Dmax ($p = .6928$).

Figure 4 shows a box-and-whiskers Tukey plot representation of changes in the planned versus IFV-reconstructed dose. The IFV reduces both the minimal and mean dose to both the PTV and the ITV. For the PTV, we obtain median values for the minimal dose D99% (Gy) = 45.2 *vs.* 48.2 Gy ($p < .0001$) and for the mean dose Dmean = 53 *vs.* 54 Gy ($p < .0001$) for the reconstructed versus planned dose values, respectively. For the ITV, the changes are less pronounced but apparent even so: the median value of D99%(Gy) decreases to 52.2 *vs.* 53.6 Gy ($p = .0007$) and Dmean also shows a slight reduction of the median value to 56 *vs.*

56.8 Gy (p = .0144). Dmax was not much affected by the IFV for neither the PTV nor the ITV (PTV: 60.3 *vs.* 60 Gy (p = .3686), ITV: 60.2 *vs.* 60 Gy (p = .5125)). Of all 61 patients in the high-risk IFV group, however, only 4 did not achieve full coverage of the prescribed dose to the ITV in the reconstructed dose. For two of those, the coverage was only moderately smaller and 95% of the ITV volume still received 48 Gy. Two patients were clear outliers (ITV-V48Gy(%) = 82.4 and 81.9%). Those were the patients for whom a δ IFV > 0.5cm was observed for 3 and 4 fractions, respectively.

Time

Positioning the patient and CBCT_1 acquisition required a median time of 7.34 min [Q1: 5.48;Q3: 9.39]. ARC1 time was 1.77 min [1.43;2.13], ARC2 was: 1.80 min [1.52;2.20]. In total, CBCT_2 acquisition, analysis, with or without couch displacement added 5.25 min [3.72;7.07] on the time per fraction. The median overall time treatment (OTT) was 8 days [6;9] and the time per fraction was 18.46 min [16.15;21.7]. Patient with an OTT ≥ 8 days (0.22 *vs.* 0.24; p = .002) or ≥ 25 min (0.22 *vs.* 0.34; p = .0003) had higher δ IFV. For the entire patient population (n=166), median CBCT_2 displacements were: 0 cm [0;0]; 0 cm [–0.2;0]; 0 cm [–0.1;0]; LR, SI, and AP, respectively. For the high-risk patient group only, 0 cm [–0.1;0.2]; -0.4 cm [–0.5;–0.1]; 0 cm [–0.4;0.3]; LR,SI,AP resulting in a median δ IFV for CBCT_2 of 0.64 cm [0.54;0.75] (Fig. 4).

Discussion

Few studies reported on IFV variability of the average tumor position [2]. To our knowledge, our studied cohort of 664 CBTs from 166 patients is the largest and most homogeneous (48 Gy in 4 fractions) reported. Such numbers provide grounds for a reliable and comprehensive evaluation of the IFV during peripheral lung SBRT. Measuring the respiration motion is mandatory for planning, but it may be insufficient for treatment delivery. Even if a 4D-CT captures tumor motion accurately, it is still only representative of the tumor motion at that particular time [5, 17]. Daily setup variations is a concern as they can modify the dose distribution in the patient [1].

The first goal of this study was to determine and characterize the actual IFV magnitude. In 105 patients (573 fractions) the IFV never exceeded 0.5 cm, with the largest motion observed in SI, followed by the AP and LR directions. Our data confirm that the IFV during lung SBRT

is mostly small (± 2 mm) and predominant in the SI direction [2, 7–10, 12, 21]. However, in 61 (36.7%) patients the IFV was ≥ 0.5 cm (91 out of 664 fractions). Our results are in agreement with previously published data reporting positional shifts occurring in 26% to 43% of patients [2, 9].

In our population, univariate analysis showed three statistically significant variables that can explain the increasing IFV (≥0.5cm): (i) lower and middle lobe lesions (53%; 48/91 fractions), (ii) patients remaining on the treatment couch ≥ 25 min (21%; 19/91 fractions) and (iii) patients having an overall-treatment-time ≥ 8 days (75%; 68/91 fractions). Tumor motion in various locations of the lungs has been described [2, 3, 8, 10, 11]. Our observations are consistent with those made by Seppenwoolde et al. and Liu et al. who found that motion was the greatest in (unfixed) lower lobe tumours [6, 15] (ii). In our population the median time per fraction was 18.46 min [16.15;21.7], which is less than the time threshold reported in literature for increased IVF (< 30–36 min) [2, 3, 9, 11, 17, 21]. Purdie et al. investigated the IFV tumor position, with an additional midpoint CBCT (8 patients, 26 fractions) [17]. They found that beyond 34 minutes, the IFV grew with a mean deviation of 5.3 mm. In 11 supine prone-treated patients Hoogeman et al. reported an increase of the standard deviation to 1.2 mm in a period of 15 min [18]. Unlike our study, time required (per part) during SBRT treatment is not specified [17]. In the same way, Nielsen et al., conclude that shorter treatment times lead to smaller IFV [10]. To properly characterize the impact of the additional CBCT, we reported the individual times required per treatment step. In our population, CBCT_2 acquisition, analysis, ± couch displacement added median 5.25 min [3.72;7.07], or 28.4%, of the median time per fraction. This surplus time on the treatment couch counteracts the increased precision we are aiming for with the extended IGRT procedure. The benefits of CBCT_2 are therefore not a given and have to be carefully balanced against the increased treatment time. Additionally, in SBRT, increasing the intra-fraction time allows for sublethal damage repair [1]. It is suggested that a fraction delivery > 30 minutes could lead to a significant reduction in tumor biologically effective dose [1]. (iii) Patients' breathing patterns can vary (magnitude/period/regularity) during treatment sessions. Those modifications may change during treatment, and between fractions [1]. Thus, it is reasonable to conclude that the increase in IFV, may be caused, at least in part, by the variability in breathing patterns (chest *vs.* abdominal, quiet *vs.* deep) or gravity acting on the lungs after the supine positioning [15]. Moreover, respiratory motion varies from day to day, target and OARs can shrink, grow, and shift in response to treatment [7]. As reducing the total time on the couch was shown to be

beneficial for the patient's positional accuracy, the benefits of intrafraction IGRT by means of a second CBCT need to be balanced against the possible loss in the patient's positional stability due to increased treatment time.

The second goal of our study was therefore to determine the dosimetric impact of the IFV (a posteriori robust evaluation). To our knowledge, no such study has yet been reported in literature. Because of the low number of treatment sessions and the high dose per fraction, a single IFV exceeding the PTV margin could result in an error that is unlikely to be recovered as the averaging process was very limited [1]. For similar reasons, concern also exists regarding the possible impact of the interplay (the simultaneous movement of internal structures and the dynamic multileaf collimator). Ong. et al. [22], however, concluded that this effect is mostly significant for single-arc, single fraction delivery at 2400 MU/min, but becomes insignificant when using at least two arcs and two or more fractions. It can therefore be ignored for the treatment conditions used in this study. Our study focuses on the dosimetric implications of intrafraction IGRT. The a posteriori reconstructions of the dose distributions that would have been delivered had no additional intrafraction positional correction been performed, showed that the CBCT_2 acquisition had limited or no beneficial impact on the ITV coverage [D99% (Gy) = 52.2 *vs.* 53.6 Gy, p = .0007; Dmean = 56 *vs.* 56.8 Gy, p = .0144; Dmax = 60.2 *vs.* 60 Gy, p = .5125] in the vast majority of the peripheral lung IGRT patients. For the low-risk group (105/166 patients), full ITV coverage would have been achieved in any case. For the 61 high-risk patients who showed at least one IFV ≥ 5 mm, a decline in PTV coverage was indeed observed, but the V48 Gy (%)-ITV coverage did not statistically change between the delivered *vs.* planned dose for all but 4 patients. Of those 4 patients, 2 still had acceptable results but 2 consistently showed IFV values ≥ 5 mm for nearly all treatment sessions (3/4 and 4/4 fractions).

We are aware of the limitations of our study. Since this is a retrospective study (2014–2019) we cannot exclude improved experience of radiation oncologist, physicist and radiation therapy technologists in managing IFV during lung SBRT. Secondly, CBCT_2 is only representative of the mid-session position of the tumor. Last but not least, intra-observer and inter-observer variability have been described in matching planning CT and CBCT, 0.9 (± 0.8) mm and 2.3 (± 1.1), respectively (2); however, our matching procedure essentially relies on auto-matching, associated with lesser inter-observer variability. Several papers have been

published on the geometrical total system uncertainty for SGRT (mechanical, imaging, registration, fusion uncertainty), the values vary between 0.5–2 mm [1].

Based on our data we demonstrated that a single CBCT is sufficient and reliable to manage the IFV. Caution must be taken in patient with lower or middle lobe lesions. Every effort should be made to ensure that patients stay on the treatment couch <25 min and have an OTT < 8 days.

As a result of the IFV shifts we observed in this study, we now employ new guidelines. It should be kept in mind that geometrical errors are planning and center specific.

Conclusion

The spatial, temporal and dosimetric target localization errors due to IFV in lung SBRT are described. A tendency for increasing IFV has been observed in three situations: patients with lower and middle lobe lesions, patients remaining on the treatment couch ≥ 25 min or patients having an OTT ≥ 8 days. The a posteriori robust evaluation showed limited and re-assuring dosimetric consequences of the IFV with respect to the ITV prescribed dose coverage. The additional midpoint CBCT could be abandoned based on these data.

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Figure.1 Treatment dose reconstruction: Original *vs*. Reconstructed plans.

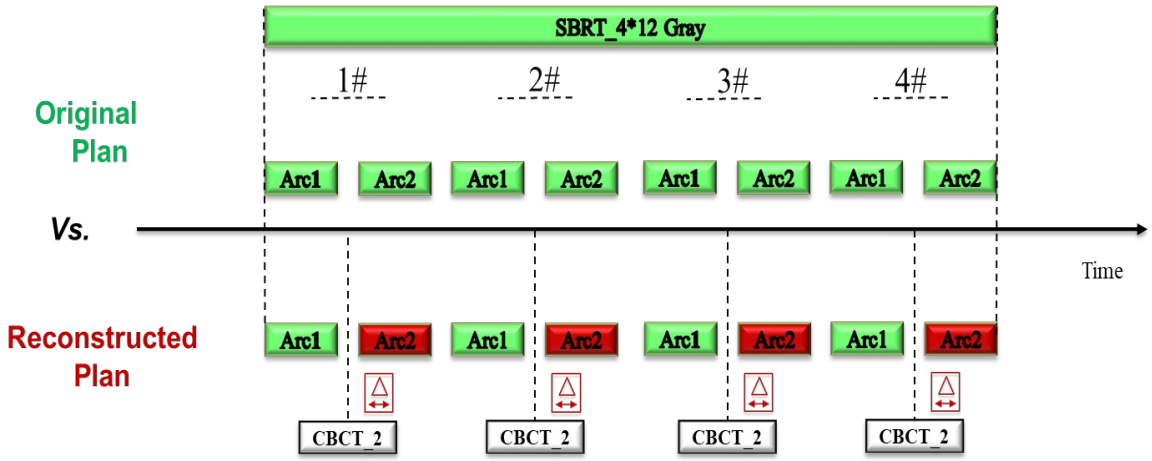

Figure 2. Session timeline and risk factors increasing intra-fractional variation.

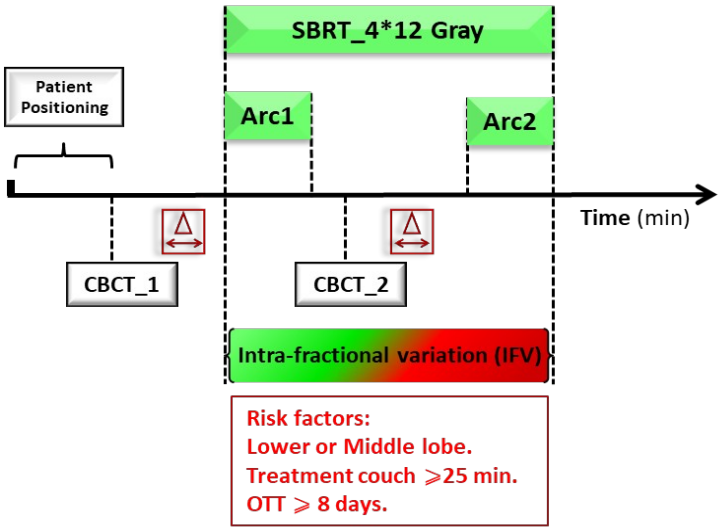

Figure 3. Summary by fractions of the three dimensions intra-fractional variation (IFV)

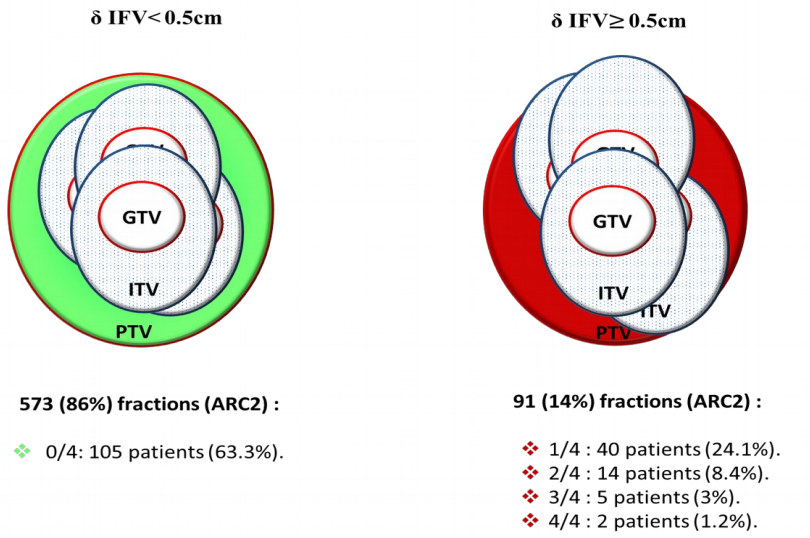

Figure 4. Box-and-whiskers Tukey plot representation of CBCT_2 displacements (X;Y;Z and 3D vector) in patients with an IFV ≥ 0.5 cm (n = 61). CBCT — cone beam computed tomography; IFV — three dimensions intra-fractional variation

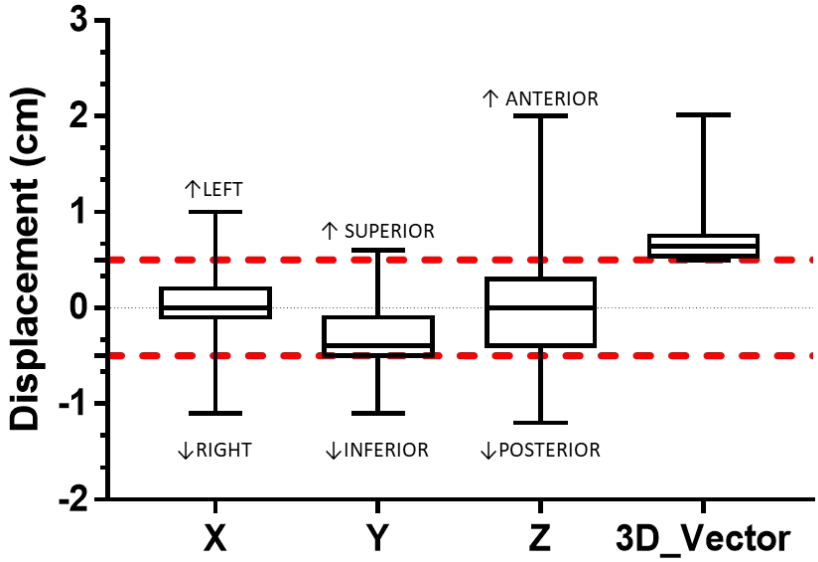

Figure 5. Box-and-whiskers Tukey plot representation of the D99 and V48 between PTV_Reconstructed *vs.* PTV_Planned (**A; C**) and ITV_Delivered *vs.* ITV_Planned (**B; D**). PTV — planning target volume; ITV — internal target volume