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M Ayadi, T. Baudier, G Bouilhol, P Dupuis, P. Boissard, et al.. Mid-position treatment strategy for locally advanced lung cancer: a dosimetric study. *British Journal of Radiology*, 2020, 93 (1110), pp.20190692. 10.1259/bjr.20190692 . hal-02948227

HAL Id: hal-02948227

<https://hal.science/hal-02948227>

Submitted on 2 Oct 2020

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Mid-position treatment strategy for locally advanced lung cancer: a dosimetric study

¹M. Ayadi, ²T. Baudier, ³G. Bouilhol, ¹P. Dupuis, ¹P. Boissard, ²R. Pinho, ²A. Krason, ²S. Rit, ¹L. Claude and ²D. Sarrut

¹ Radiotherapy and Physics Department, Leon Berard Cancer Center, 28, rue Laennec F-69373, Lyon, France

² Univ Lyon, INSA-Lyon, Université Lyon 1, CNRS, Inserm, Centre Léon Bérard, CREATIS UMR 5220, U1206, F-69373, Lyon, France

³ Department of Radiotherapy, Hartmann Radiotherapy Center, American Hospital of Paris, Neuilly, France

Br J Radiol 2020; 93: 20190692.

Abstract

Objectives

The internal target volume (ITV) strategy generates larger planning target volumes (PTVs) in locally advanced non-small cell lung cancer (LA-NSCLC) than the Mid-position (Mid-p) strategy. We investigated the benefit of the Mid-p strategy regarding PTV reduction and dose to the organs at risk (OARs).

Methods

44 patients with LA-NSCLC were included in a randomized clinical study to compare ITV and Mid-p strategies. GTV were delineated by a physician on MIP images and on Mid-p images from four-dimensional CTs. CTVs were obtained by adding 6mm uniform margin for microscopic extension. CTV to PTV margins were calculated using the van Herk's recipe for setup and delineation errors. For the Mid-p strategy, the mean target motion amplitude was added as a random error. For both strategies, 3D conformal plans delivering 60 to 66Gy to PTV were performed. PTVs, dose-volume parameters for OARs (lung, esophagus, heart, spinal cord) were reported and compared.

Results

With the Mid-p strategy, the median of volume reduction was 23.5cm³ (p=0.012) and 8.8cm³ (p=0.0083) for PTV_T and PTV_N respectively; the median mean lung dose (MLD) reduction was 0.51Gy (p=0.0057). For 37.1% of the patients, delineation errors led to smaller PTV with the ITV strategy than with the Mid-p strategy.

Conclusion

PTV and MLD were significantly reduced using the Mid-p strategy. Delineation uncertainty can unfavorably impact the advantage.

Advances in knowledge

To the best of our knowledge, this is the first dosimetric comparison study between ITV and Mid-p strategies for LA-NSCLC. Mid-p strategy significantly reduces tumor, nodal PTVs and MLD.

1 Introduction

Treating locally advanced non-small cell lung cancer (LA-NSCLC) remains challenging with reported 5-years survival rates around 10-20% [1]. Radiotherapy with prescribed doses of 60-66 Gy in 30-33 fractions, combined or not with chemotherapy, is the standard of care [2]. A critical problem in LA-NSCLC treatment is the tumor motion caused by patient breathing. Tumor motion leads to the use of large internal margins to define the Planning Target Volume (PTV) [3], potentially increasing normal lung toxicity.

Several breathing compensation methods, of variable complexity, are available and can be divided into two groups: active or passive techniques [4]. The most common passive technique is the Internal Target Volume (ITV) strategy [3]. Its simplicity has made it the preferred strategy but it is a "maximalist" approach because it is obtained by merging the Gross Tumor Volumes (GTV) of all breathing phases. The ITV is typically delineated on the Maximum Intensity Projection (MIP) CT image reconstructed from a four-dimensional (4D) CT image [5]. An innovative passive strategy introduced by Wolthaus *et al.* [6] is the Mid-position (Mid-p) strategy. Unlike the ITV strategy which uses fixed margins, the Mid-p strategy consists in planning the treatment on the time-averaged position of the breathing cycle described by the 4D CT image, with patient-specific margins depending on the amplitude of the tumor motion. This approach theoretically leads to a reduction of the PTV and, therefore, a reduction of the irradiated volume of normal tissues; up to 15% according to [7]. The same, Wanet *et al.* [8] recommended this technique for large tumors (> 1.5cm). Most of the studies in the literature focused on early-stage NSCLC treated by stereotactic body radiotherapy treatment for Mid-p [8] or Mid-ventilation (approximation of the Mid-p) [9] [10].

From October 2012 to May 2018, patients at our institution with LA-NSCLC were included in a phase 2 randomized study comparing the ITV strategy (control arm) with the Mid-p strategy. Here, the objective is to evaluate the dosimetric potential benefit of the Mid-p strategy with respect to the ITV strategy on a prospective trial for patients treated with conventional fractionated radiotherapy. In this paper, we only focus on dosimetric aspects: the PTV reduction with the Mid-p strategy and the benefits in terms of organ at risk (OAR) dose reduction (clinical aspects are not considered).

2 Patients and methods

2.1 Image acquisition and processing

44 patients with LA-NSCLC were included in a phase 2 randomized clinical trial to compare ITV and Mid-p strategies (16 were included in the ITV arm and 28 in the Mid-p arm). Those patients were setup either in an alpha cradle mold (Alpha Cradle Molds, Akron, USA) or in a BlueBAGTM (Medical Intelligence, Schwabmuenchen, Germany), arms above the head. For each patient, a 4D CT image was acquired under normal free breathing with a Phillips Brilliance Big Bore (Philips Medical System, Cleveland, USA) using a 2 mm slice width and the Pneumo Chest bellows belt. The pitch was adapted from 0.06 to 0.08 according to the patient breathing pattern. A ten-phases 4D CT image was reconstructed based on the respiratory signal phase. The blurred average, the MIP and the Mid-p images were automatically computed in house developed software. The MIP image was computed projecting the 4D image along the time axis and the Mid-p image was generated with Elastix, a deformable registration software [11]. The 50% image (maximum exhale) was registered to the other nine phases using B-splines registration [12]. Sliding motion between the lungs and the rib-cage was accounted for with the motion mask strategy [13] when its automated segmentation was successful from a visual assessment, otherwise with an automated lung segmentation. If none of the two segmentations was successful, sliding motion correction was disabled. From the nine vector fields, the time average position (Mid-p) was computed and each phase image was warped towards the Mid-p. The median of these ten warped images was computed to finally

generate the Mid-p image. A physicist and an expert in image processing visually validated all Mid-p images.

2.2 Treatment plan

Radiation oncologists delineated up to four tumor volumes for each patient on MonacoTM version 5.11.02 (Elekta Oncology Systems, Crawley, West Sussex, UK): GTV_T (the primary tumor) and GTV_N (in case of nodal disease) on the Mid-p image, and internal GTV_T (IGTV_T) and internal GTV_N (IGTV_N) on the MIP image. The primary tumor was delineated using a preset lung window and the lymph nodes were delineated using a preset soft tissue window. Heart, spinal cord, esophagus, brachial plexus, lungs were delineated as OARs on the average image used for the treatment plan. The clinical target volumes, CTV and ICTV, were obtained adding a 6 mm margin in all directions to the GTV and IGTV, respectively, to account for the sub-clinical disease [14]. The planning target volumes, PTV and IPTV, were obtained using van Herk's formula (assuming that the dose delivered to the CTV was at least 95% of the prescribed dose and for 90% of the population) including systematic Σ and random σ errors [15] [16]:

$$\text{Margin} = 2.5 \Sigma + 1.64 \sqrt{\sigma^2 + \sigma_p^2} - 1.64 \sigma_p \quad (1)$$

with a penumbra width $\sigma_p = 6.4$ mm for lung treatment [10] [17]. For both Mid-P and ITV, the systematic errors Σ and the random errors σ considered positioning and delineation errors extracted from the literature [18] [19] (Table 1). Mid-P additionally included a random uncertainty for breathing motion equal to 36% of the peak-to-peak amplitude in all three directions [16]. Amplitudes were extracted in all volumes from deformation vector fields (DVF) obtained from the deformable registration.

	Systematic Σ			Random σ		
	LR	CC	AP	LR	CC	AP
Delineation [mm]	4.0	4.0	4.0	-	-	-
Positioning [mm]	1.3	1.7	1.4	2.7	3.5	2.4
Breathing [mm]	-	-	-	0.36A	0.36A	0.36A

Table 1: Systematic and random uncertainties in the 3 directions for margin calculation;
A: amplitude, LR: left right, CC: cranio-caudal, AP: anterior posterior.

A three-dimensional conformal radiation therapy (3DCRT) treatment plan was planned for each strategy (ITV and Mid-p) on the average image using 8 to 10 static fields of 6~MV photon beams. Treatment plans for both arms were calculated using one of the two following B-type algorithm, the Superposition algorithm (XiOTM, CMS Inc., Saint Louis, US) or the Collapse Cone algorithm (MonacoTM); a satisfying accordance was found in terms of dose calculation performance in inhomogeneous tissues between both algorithms [20]. The total prescribed dose to the PTV varied from 60 Gy to 66 Gy in 30 to 33 fractions depending on dose constraints reported by the French Radiotherapy Society [21]. Patients were all treated on a SynergyTM linear accelerator (Elekta Oncology Systems, Crawley, West Sussex, UK) with cone-beam CT image-guidance. The positioning uncertainty reported in Table 1 relies on cone-beam CT acquired for the three first sessions and then once a week [19].

2.3 Treatment plans analysis

For all patients, tumor amplitude (GTV_T , GTV_N) and calculated margins volumes were reported. Various dosimetric parameters defined by the clinical trial protocol were also reported: the dose received by 95% of the PTV (D_{95}), the maximum dose (D_{max}) received by the spinal cord and the brachial plexus, the mean lung dose (MLD), the volume of lung (*i.e.* lungs minus PTVs) receiving at least 5 Gy, 20 Gy, and 30 Gy (V_5 , V_{20} , V_{30}), the volume of esophagus receiving at least 55 Gy (V_{55}), the mean dose received by the heart (D_{mean}), and the volume of heart receiving at least 40 Gy (V_{40}).

3 Results

3.1 Patient characteristics

The first 35 patients out of the 44 included patients were selected for this dosimetric analysis. Five patients were excluded due to poor 4D CT image quality, treatment modality change (modification for intensity modulated delivery due to extremely large tumor volume $> 1150 \text{ cm}^3$), or cancelled treatment (intercurrent disease). Four other patients due to incomplete data. 74.3% of the patients were men. The mean age was 66.0 years with a standard deviation (SD) of 6.5 years. 48.6% of the patients had both parenchymal (or bronchial) and nodal diseases. The mean (range) GTV_T volume was 76.5 cm^3 (1.7 to 284.3 cm^3), GTV_N volume was 26.7 cm^3 (1.4 to 106.7 cm^3), $IGTV_T$ volume was 87.7 cm^3 (2.2 to 298.9 cm^3), $IGTV_N$ volume was 29.4 cm^3 (1.6 to 110.8 cm^3). The mean (range) PTV_T volume was 467.8 cm^3 (83.8 to 1109.7 cm^3), PTV_N volume was 269.7 cm^3 (98.3 to 545.6 cm^3), $IPTV_T$ volume was 492.1 cm^3 (87.0 to 1069.9 cm^3), $IPTV_N$ volume was 383.3 cm^3 (118.0 to 574.4 cm^3).

3.2 Tumor amplitude

GTV_T and GTV_N amplitude statistics in all directions are shown in Figure 1. The median GTV_T amplitudes were 3.7 mm antero-posterior (AP), 3.0 mm left right (LR), 6.2 mm cranio-caudal (CC) and the maximal GTV_T amplitude was 27.8 mm CC. 25.7% of the patients had a tumor amplitude larger than 10 mm CC. The median GTV_N amplitudes were 3.3 mm AP, 2.8 mm LR, 5.5 mm CC, and the maximal GTV_N amplitude was 10.7 mm CC.

3.3 Calculated margins for both strategies

ICTV to IPTV calculated margins were fixed among patients: 11.3 mm AP, 11.4 mm LR and 12.3 mm CC. Calculated margins for Mid-p strategy are presented in Figure 2. The median of margins added to CTV_T were 11.5 mm AP, 11.5 mm LR, 12.9 mm CC, with a maximal margin of 20.7 mm in CC. For CTV_N , the median of margins were 11.5 mm AP, 11.5 mm LR, 12.8 mm CC, with a maximal margin of 13.9 mm in CC.

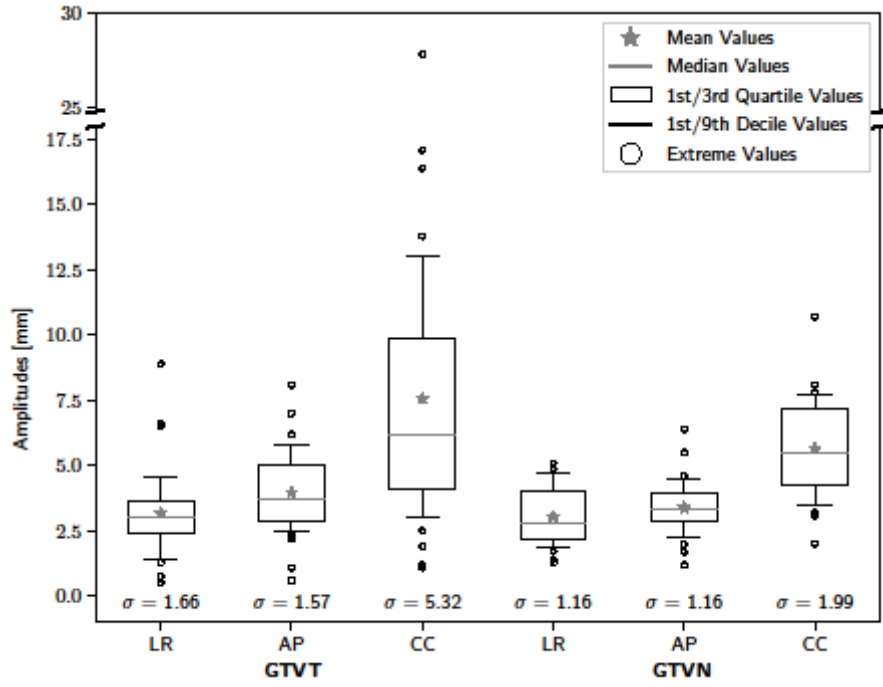


Figure 1: Mean, median, min-max amplitudes for GTVT and GTVN in the 3 directions.

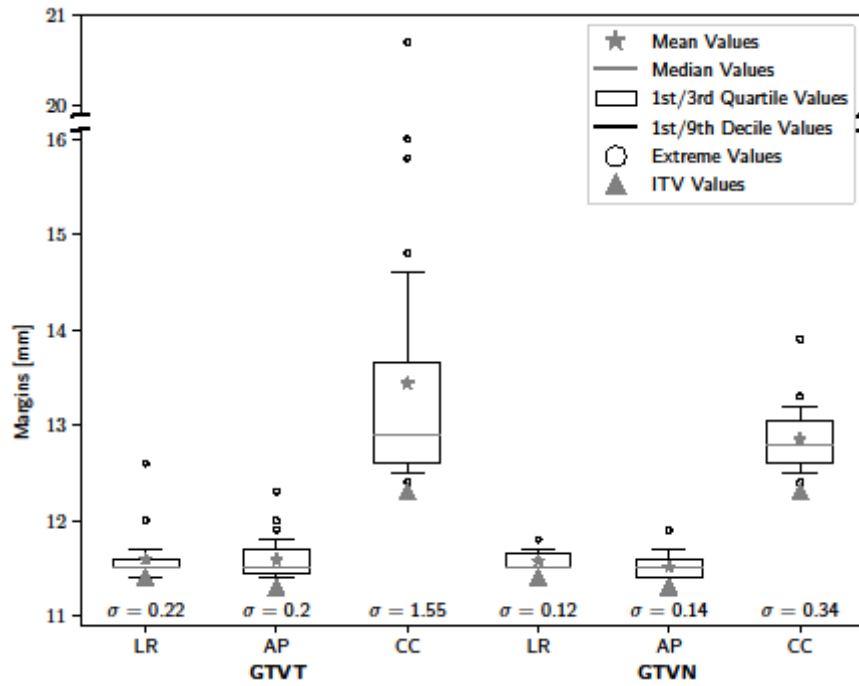


Figure 2: Calculated margins for tumor and nodes in the Mid-p strategy in the three directions.

3.4 Volume reduction

The Mid-p strategy led to smaller PTV_T and PTV_N for 62.9% patients. The volume differences and corresponding statistics are presented for all patients in Figure 3. The median of volume reductions between $IPTV_T$ and PTV_T was 23.5 cm^3 ($p = 0.012$) and the one between $IPTV_N$ and PTV_N was 8.8 cm^3 ($p = 0.0083$).

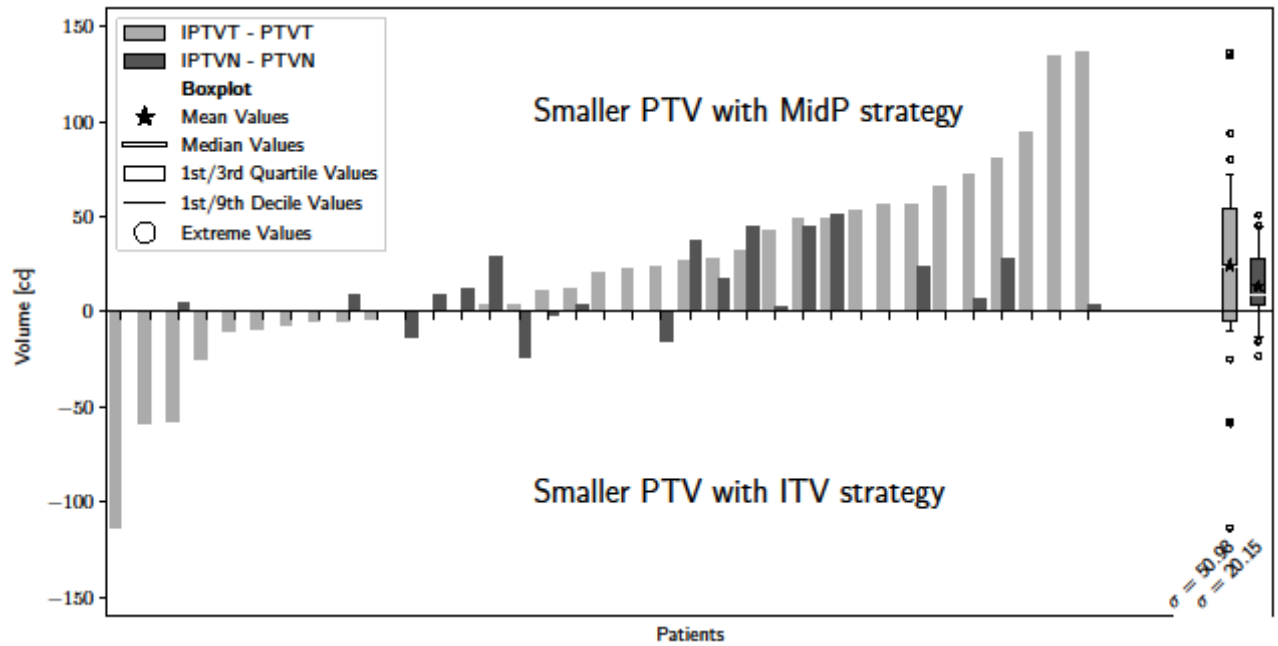


Figure 3: Volume differences for tumor and nodes for all patients and boxplots for all patients on the right. The patients are sorted from the smallest to the largest $IPTVT - PTVT$ values.

3.5 Dosimetric evaluation

For the patient cohort, the mean prescribed dose was 63.9 Gy and the mean (range) PTV D_{95} was 92% (82% to 97%). Between the ITV and the Mid-p plans, the differences in terms of dosimetric parameters for OARs have been listed in Table 2. A notable result in terms of mean difference (SD) was 0.51 Gy (1.0 Gy, $p = 0.0057$) for the MLD and positive for 71% of patients.

		Difference ITV – Mid-p for all patients				
		mean	σ	min	max	p
Lung	D_{mean} [Gy]	0.51	1.0	-1.6	3.3	$5.7 \times 10^{-3} *$
	V_5 [cm ³]	43.0	122.1	-172.0	396.0	$4.8 \times 10^{-3} *$
	V_{20} [cm ³]	34.3	85.9	-210.5	246.8	$2.6 \times 10^{-3} *$
	V_{30} [cm ³]	24.6	57.3	-73.6	230.3	$1.7 \times 10^{-3} *$
Esophagus	V_{55} [cm ³]	-0.53	5.8	-33.45	4.4	5.9×10^{-1}
Heart	D_{mean} [Gy]	0.65	2.7	-5.2	9.8	1.7×10^{-1}
	V_{40} [%]	0.37	3.1	-8.1	5.3	5.0×10^{-1}
Spinal cord	D_{max} [Gy]	0.33	1.3	-1.8	4.7	1.3×10^{-1}
Brachial plexus	D_{max} [Gy]	-1.6	2.6	-6.4	0.7	2.7×10^{-1}

Table 2: Difference between ITV plan and Mid-p plan in terms of dose received by OARs.

* means significant results with $p < 0.01$.

4 Discussion

4.1 GTV volumes

The GTV and IGTV sizes for the patient cohort shown in 3.1 were similar to [7] [8], mean GTV_T and GTV_N volumes were smaller on average than mean $IGTV_T$ and $IGTV_N$ volumes. This difference between GTV_T and $IGTV_T$ volumes is consistent with previous studies [22]. GTV volume should be close to the tumor volume obtained from a single breathing phase while the IGTV volume encompassed all the tumor positions during the patient breathing. We noticed that for 4 patients, the GTV_T is larger than the $IGTV_T$, and 3 for GTV_N . For two of these patients with a GTV_T larger for the Mid-p strategy than for the ITV strategy, this can be explained by contouring uncertainties. Indeed, visual analysis showed that tumors were in the bronchial area (or located close to the mediastinum) with poor contrast leading to difficulties for delineation [22]. For the other patients, the difference was due to inconsistent contours, mainly at the tumor boundaries. Similarly, for the nodal volumes, low contrast in mediastinum increased the delineation uncertainty, independently of Mid-p or MIP image [22]. In these particular cases, a positron emission tomography (PET) and/or magnetic resonance imaging (MRI) would have probably helped in reducing delineation uncertainty [23] [24] [25] [26].

4.2 Tumor amplitude

Like observed in previous studies [27] [28], the largest component of the lung tumor and nodes motions was in the CC direction. The median peak-to-peak amplitudes were similar for both (GTV_T and GTV_N) with 6.5 mm and 6.0 mm, respectively. These results are comparable to those reported by Schaake *et al.* [29]. The maximum peak-to-peak amplitude for the GTV_T was much larger than that of the GTV_N (27.8 mm vs 10.7 mm) because this GTV_T was located in the left inferior lobe, a common behavior for tumors close to the diaphragm.

4.3 PTV and margins

The mean PTVT and PTVN volume reductions were 6.5% and 6.8% respectively. Wolthaus *et al.* found 15% of reduction for various stages of lung cancer [7]. On one hand, the differences could be explained by a large SD (10.5% for PTV_T and 8.7% for $IPTV_T$) in this study. On the other hand, their methodology was different: no CTV margins were used, an ITV motion expansion was used to determine the $IPTV_T$ (GTV_T plus half of the peak-to-peak tumor amplitude), the periodic motion uncertainty was one third of the amplitude and the patient repositioning systematic and random uncertainty values were different due to a different protocol. In our study, the IGV_T was delineated with the MIP image exclusively. The difference of PTV volume reduction between our study and Wolthaus *et al.* could be partly explained by the difference between ITV margins and Mid-p margins. Considering the example given in [7] of a peak-to-peak tumor motion of 15 mm in CC direction and an off-line setup correction, we obtain with our uncertainty values, a margin of 19.8 mm for ITV strategy and 15.3 mm for Mid-p strategy (versus 20.2 mm and 14.9 mm respectively in [7]).

For 62.9% of the patients, the PTV_T volume was significantly smaller than the $IPTV_T$. This difference was less important than with the GTV_T (88.6%). For the patients with larger PTV in the Mid-p strategy compared to the $IPTV$ in the ITV strategy (patients with negative values in

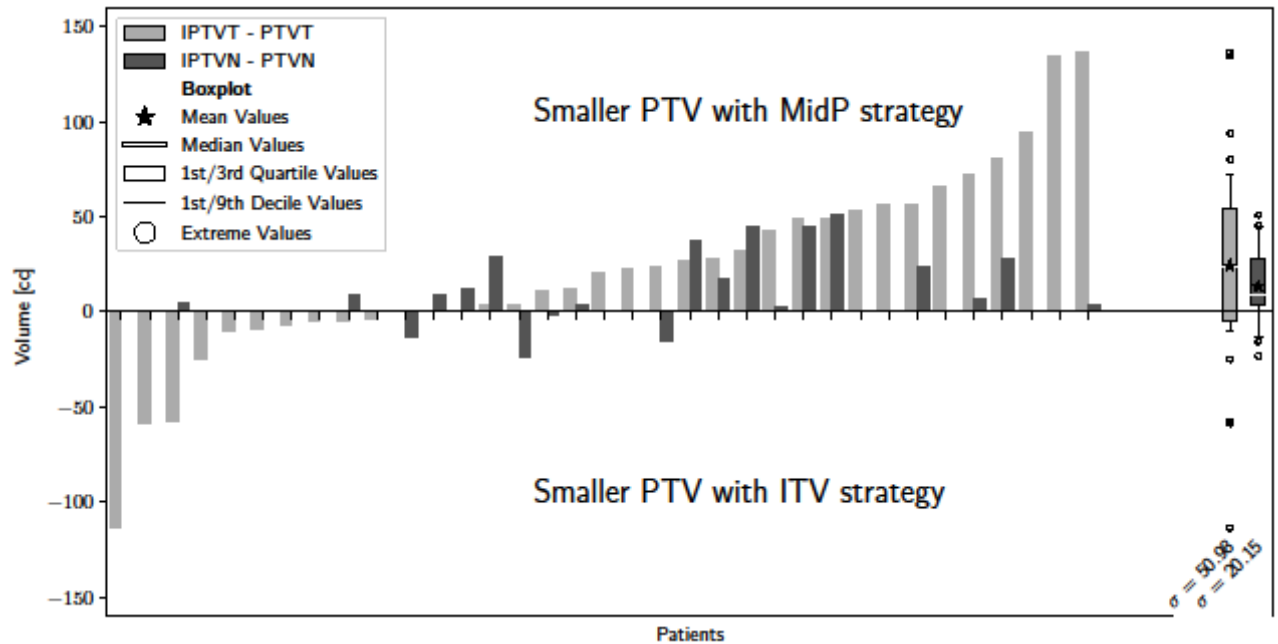


Figure 3), the delineation errors were predominant.

4.4 Dosimetric analysis

For 9 patients, margins have been reduced to respect the OAR dose constraints and in most cases, the tumor motion amplitude was larger than 10 mm in the CC direction. To our knowledge, no clinical study has been dedicated to the dosimetric comparison of different motion management strategies. With the Mid-p strategy, the mean MLD reduction was 0.51 Gy. The results corroborate Ehrbar's results [30]; a strategy change involving a PTV reduction leads to a MLD diminution. As MLD is correlated to lung toxicity, a clinical benefit could be expected in the medium term [31]. Among all patients, the minimum PTV D_{95} was 82%. This unsatisfying coverage was in that case due to the plexus brachial proximity. Moreover, during the study, a dose calculation algorithm change in our department mainly led to a decrease of the PTV coverage; but it did not affect the intra patient results. Concerning the mean heart dose, it was reduced by 0.65 Gy with the Mid-p strategy. Given that the overall survival for LA-NSCLC is poor and that patients frequently have co-morbidities that increase heart disease risks, cardiac late toxicities related to radiotherapy are difficult to describe. Recently, Speirs *et al.* [32] showed that the heart dose was correlated with the overall survival (especially $V_{50} > 25\%$) and the cardiac toxicity. In our patient cohort, the mean heart V_{40} was less than 12.2% for both strategies and the larger heart V_{40} difference for one patient between MIP and Mid-p strategy was 5.3% (5.4% vs 0.1% respectively). In this latter case, this difference could be explained by non-reproducibility in delineation: the IGTV_T inferior edge was delineated closer to the heart compared to the GTV_T one.

From a general point of view, inverse planning and intensity modulated radiation therapy would have further increased the benefit of Mid-p strategy by improving PTV coverage while minimizing the dose received by OARs [33] [34] [35]. These treatments planning strategies would have been applicable to the presented cohort because the interplay effect is negligible [36].

4.5 Limitations

The 4D CT image is based on one average respiratory cycle so it is sensitive to irregularities of the patient breathing. Breathing motion artifacts can lead to GTV size errors. For this study, the breathing pattern of each patient was systematically checked on the 4D CT reconstruction before clinical use. In case of large amplitude variations in the respiratory trace

and artifacts at the level of the tumor, a second 4D CT image was acquired. Only one patient was excluded from the study due to poor image quality.

To be in agreement with our current clinical practice, the Mid-p and MIP target volumes were delineated independently by a single radiation oncologist leading to a delineation variability in our study. Patients with better ITV strategy than Mid-p strategy had larger GTV_T than IGTV_T due to clear inconsistent delineations. Consequently, for the latter cases, PTV_T were larger than IPTV_T in Figure 3. Methodologies to reduce this uncertainty should be considered, e.g., a double-check delineation for quality assurance, a contour propagation from Mid-p to ITV, a better definition of the nodes or nodes area that need to be irradiated.

The same penumbra $\sigma_p = 0.64$ cm in equation $Margin = 2.5 \Sigma + 1.64 \sqrt{\sigma^2 + \sigma_p^2} - 1.64 \sigma_p$ (1) was used for both tumor and nodes in the margin recipe to simplify the margin calculation process. For nodes in the mediastinum, a σ_p of 0.32 cm may have been used because the penumbra in soft tissues is narrower [17]. In the same way, Σ in equation $Margin = 2.5 \Sigma + 1.64 \sqrt{\sigma^2 + \sigma_p^2} - 1.64 \sigma_p$ (1) could be reduced using a daily cone beam CT (CBCT) by nullify the systematic setup error for the tumor [37]. However, Rit *et al.* [38] shown that the variability of breathing amplitude have a limited impact on the margins.

5 Conclusion

This dosimetric study aimed at comparing PTVs and doses received by OARs for two passive breathing compensation methods, the ITV strategy and the Mid-p strategy, for patients with LA-NSCLC treated with 3DCRT. The Mid-p strategy leads to significant target volume and MLD reduction even if delineation uncertainties unfavorably impacted the Mid-p advantage for one third of the patients. The benefit of the Mid-p strategy over the ITV strategy has to be confirmed with the clinical analysis of local tumor control and toxicity reduction.

6 Acknowledgment

This work was partly supported by the SIRIC LYriCAN: INCa-DGOS-Inserm_12563.

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