Original Article

# Is Maximum Intensity Projection an Optimal Approach for Internal Target Volume Delineation in Lung Cancer?

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## Abstract

**Purpose:** Respiratory-induced tumor motion is a major challenge in lung cancer (LC) radiotherapy. Four-dimensional computed tomography (4D-CT) using a maximum intensity projection (MIP) dataset is a commonly used and time-efficient method to generate internal target volume (ITV). This study compared ITV delineation using MIP or tumor delineation on all phases of the respiratory cycle. **Materials and Methods:** Thirty consecutive patients of LC who underwent 4D-CT from January 2014 to March 2017 were included. ITV delineation was done using MIP ($ITV_{MIP}$) and all ten phases of the respiratory cycle ($ITV_{10Phases}$). Both volumes were analyzed using matching index (MI). It is the ratio of the intersection of two volumes to the union of two volumes. A paired sample *t*-test was used for statistical analysis, and $P < 0.05$ was considered statistically significant. **Results:** The mean ± standard deviation volume of $ITV_{10Phases}$ was significantly larger compared to $ITV_{MIP}$ (134 cc ± 39.1 vs. 113 cc ± 124.2, $P = 0.000$). The mean MI was 0.75 (range 0.57–0.88). The mean volume of $ITV_{10Phases}$ not covered by $ITV_{MIP}$ was 26.33 cc (23.5%) and vice versa was 5.51 cc (6.1%). The mean MI was 0.73 for tumors close to the mediastinum, chest wall, and diaphragm. MI was not different between tumors ≤5 cm and >5 cm. The average time required for delineation was 9 and 96 min, respectively. The center of mass of two ITVs differed by 0.01 cm. **Conclusion:** ITV using MIP is significantly smaller and may miss a tumor compared to ITV delineation in 10 phases of 4D-CT. However, the time required is significantly less with MIP. Caution should be exercised in tumors proximity to the mediastinum, chest wall, and diaphragm.

**Keywords:** Four-dimensional computed tomography scan, internal target volume, lung cancer, maximum intensity projection

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## Introduction

Respiratory motion is an important uncertainty factor for target volume delineation in lung cancer (LC) radiotherapy (RT).[1] Motion management is essential to reduce the margins given to account for respiratory motion of moving target and to reduce the dose to uninvolved lung parenchyma.[2] Various techniques are available for motion management in RT, which includes motion-encompassing methods such as slow computed tomography (CT) scans, four-dimensional CT (4D-CT), respiratory gating, breath-hold, and tumor-tracking.[3] 4D-CT/respiration-correlated CT is the most commonly used motion encompassing technique for internal target volume (ITV) delineation and thereby estimating individual margins for tumor motion.[4,5]

The ITV accounts for geometric uncertainties due to internal variation in tumor position, size, and shape.[6] 4D-CT scanners temporally correlate respiratory information and CT acquisition, resulting in one CT dataset. 4D-CT dataset typically comprises CT dataset related to 10 respiratory phases. ITV can be generated by delineating tumors in each of the 10 datasets. Combining all of these gives one volume which gives information about tumor motion. However, this process is time-intensive and difficult to implement for every patient in a busy center. Postprocessing software can provide us with a single 3D-CT dataset such as maximum intensity projection (MIP), average intensity projection (AveIP), and mid ventilation phases.[7-9] The MIP is a 3D-CT dataset where each voxel represents the highest intensity along the viewing ray of each pixel of volumetric data. One of the advantages

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of the MIP technique is that it gives a reasonable correct estimation of tumor motion in less time. MIP is shown to be reliable in the peripheral stage I–II lung tumors treated with stereotactic RT.[10] Limitations of the MIP dataset is its inaccuracies in estimating actual tumor motion and delineating tumor precisely adjacent to high-density structures, such as chest wall, diaphragm, and mediastinum.[11] Edges between tumor and high-density structures get blurred on the MIP images, and so, the extent of disease may be underestimated or overestimated on the MIP depending on individual scenarios.[12,13]

Other techniques such as delineating tumor in AveIP datasets, midventilation dataset, two extreme phases (end inspiration and end expiration), and 3–4 phases of respiration have been used for ITV generation in early-stage LC.[9,11,13,14] The time required for contouring tumors in all 10 phases or multiple phases of 4D-CT is the most significant drawback for adopting this approach in high-volume centers.[9] Some studies have compared MIP and all 10 phases for tumor delineation with small primary tumor in early-stage LC, which would relatively take less time to contour in all 10 phases.[9] Very few studies with small patient numbers compared both these techniques in locally advanced LC where it could have a maximum impact in delineation uncertainity.[10,11]

In this study, we have included consecutive patients of all stages of LC (early and locally advanced) and compared two different techniques for ITV generation: (1) primary tumor delineation on the MIP dataset and (2) on all ten phases of the respiratory cycle. The main objectives were to compare the two volumes with each delineation technique and also to compare the two techniques with respect to tumor size and proximity to adjacent structures and document the time required for contouring with both the techniques.

## Materials and Methods

The gross tumor volume delineation was done retrospectively in 30 consecutive LC patients who underwent 4D-CT for their radical RT treatment planning from January 1, 2014, till March 31, 2017. This study was approved by an institutional review board of Tata Memorial Hospital, and a waiver of consent was obtained.

### Image acquisition

Patients were positioned on an RT couch with appropriate immobilization devices and three radiopaque markers (fiducials) at the level of xiphisternum. A block containing six infrared-reflecting markers was placed on the patient, midway between the xiphisternum and umbilicus to track the respiration. The motion of the infrared-reflecting marker was captured by a camera fixed to the end of the treatment couch, and a respiratory signal was displayed in the control room. First free-breathing (FB) CT scan was taken with intravenous contrast on a GE scanner of a wide-bore 16-slice CT system. After FB CT, 4D-CT scan acquisition was done using Varian Real-time Position Management (RPM) system. Entire thorax from apex to lung base was selected for 4D-CT acquisition as per the institutional protocol. Scan parameters were set at 120 kV, 30 mA, and slice thickness of 2.5 mm. After the 4D-CT acquisition, images were retrospectively binned into 10 different phases of the respiratory cycle and the MIP CT dataset was generated using Advantage Workstation 4.1. FB CT and 4D-CT datasets were then transferred to the Varian Eclipse Treatment Planning System (Varian Medical System, Palo Alto, CA, USA).

### Internal target volume delineation

The gross tumor volume (GTV) was delineated by an experience Radiation Oncologist (SB) on standard mediastinal (W/L - 350/40) and lung window setting (W/L-1500/-500). First it was done the MIP dataset and later on each phase of respiratory cycle. The contours were subsequently reviewed by a senior radiation oncologist (JPA) for its correctness. The target volume contoured on the MIP dataset was labeled as $ITV_{MIP}$. The GTV was contoured on each of the 10 phase CT datasets (Phase 0–Phase 90) individually to create 10 GTVs (GTV0 … GTV90), respectively. To produce a composite structure, each phase CT dataset had to be registered with a reference CT dataset; here, the MIP dataset was used as a reference image dataset. The GTVs from each phase (GTV0 … GTV90) were copied on the MIP CT dataset to produce a composite structure and labeled as $ITV_{10Phases}$ [Figure 1].

Thereafter, overlapping and encompassing volumes between the two ITVs were generated, and the matching index (MI) was used to compare $ITV_{MIP}$ and $ITV_{10Phases}$. MI is the ratio of the intersection of two volumes to the union of two volumes.[11] The ideal MI should be 1, but a value of ≥0.8 is considered a good agreement between the two ITV generation techniques, as reported in the literature.[14,15] Dice similarity coefficient index (DSI) was also determined to see the agreement between the two volumes, $ITV_{10Phases}$ and GTV of individual phase of 4D-CT. It is the ratio of twice the overlap volume by the union of the two volumes. It was derived directly from

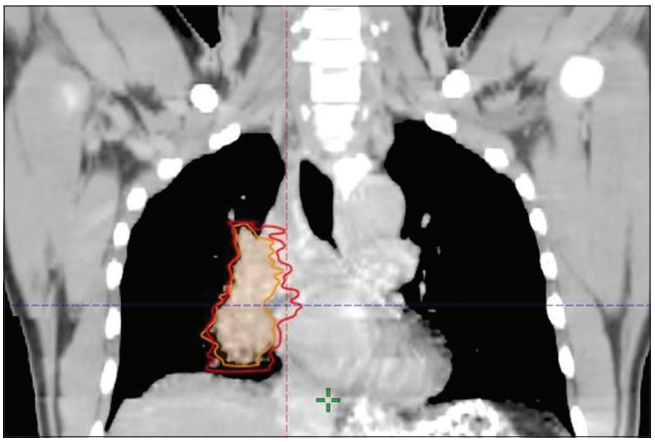

**Figure 1:** Coronal image of maximum intensity projection dataset showing internal target volume contour delineated using maximum intensity projection (red color) superimposed with composite structure of internal target volume delineated using all 10 phases (orange color)

treatment planning system by generating tables and graphs in the statistic tool of the 4D planning. DSI is useful to compare $ITV_{10Phases}$ with individual phase GTV to correlate most similar individual phase GTV with the $ITV_{10Phases}$ for tumors which are in proximity to the chest wall, the diaphragm, and the mediastinum. The time required for delineating $ITV_{MIP}$ and $ITV_{10Phases}$ was noted separately.

The center of mass (COM) coordinates of the $ITV_{MIP}$ and $ITV_{10Phases}$ was recorded in the *x* (left-right), *y* (anterior-posterior), and *z* (superior-inferior) coordinates on the treatment planning system from the three fiducials kept on the patient during scanning. The negative sign indicates a shift toward inferior, left, and posterior direction, and a positive sign indicates the superior, right, and anterior direction. The 3D centroid was calculated according to the below formula. 3D centroid shifts were calculated by calculating the difference between the 3D centroid of the two ITVs.

$$\text{3D centroid} = \sqrt{LR^2 + AP^2 + CC^2}$$

The location of the tumor adjacent to the chest wall, the diaphragm, and the mediastinum was noted for the accuracy of $ITV_{MIP}$ in such tumors. As this was an exploratory study on techniques of primary target volume delineation alone, the nodal volumes were not contoured for this study.

### Statistical analysis

The $ITV_{MIP}$ and the $ITV_{10Phases}$ volumes were compared using MI. Values of MI ≥0.8 were considered as a very strong correlation, 0.6–0.8 as strong correlation, and <0.6 as weak correlation. The volume of $ITV_{MIP}$ not covered by $ITV_{10Phases}$ and vice versa was also calculated. Wilcoxon signed-rank test was used to compare the difference between the two ITVs and their 3D centroid shift, and a $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS software version 21.0 (SPSS Inc., Chicago, IL, USA).

## Results

The clinicopathological details of the patients and the tumor included in the study are described in Table 1. The median age of the cohort was 60 years (range 42–79 years). Of 30 patients, 19 had tumor size ≤5 cm and 11 had tumor size >5 cm. Tumors close to high-density structures such as mediastinum, chest wall, and diaphragm were 15. Individual patient characteristics are outlined in Table 2.

### Volumes and matching index

For all patients, the $ITV_{10Phases}$ volume was larger than the $ITV_{MIP}$ as shown in Table 3. The mean $ITV_{10Phases}$ volume was 134.2 cc (range 13–627 cc) and $ITV_{MIP}$ volume was 113.4 cc (range 11–569 cc). The mean ratio (±standard deviation [SD]) of $ITV_{10Phases}$ and $ITV_{MIP}$ was 1.19 (±0.16). The Wilcoxon signed-rank sum test showed that there was a statistically significant difference between $ITV_{10Phases}$ and $ITV_{MIP}$ volume ($P \leq 0.001$).

**Table 1: Patient and tumor characteristics**

| Characteristics | *n* (%) |
|---|---|
| Gender | |
| Male | 25 (83) |
| Female | 5 (17) |
| T stage | |
| T1-T2 | 13 (43) |
| T3-T4 | 17 (57) |
| Lobe | |
| Upper | 20 (67) |
| Middle | 4 (13) |
| Lower | 6 (20) |
| Laterality | |
| Right | 21 (70) |
| Left | 9 (30) |
| Proximity | |
| Chest wall | 5 (17) |
| Diaphragm | 1 (3) |
| Mediastinum | 8 (27) |
| Chest wall + diaphragm | 1 (3) |
| Histology | 17 (57) |
| Adenocarcinoma | 17 (57) |
| Squamous | 9 (30) |
| Small cell | 4 (10) |

The mean of the overlap volume between $ITV_{MIP}$ and $ITV_{10Phases}$ for all patients was 108 cc (range 9–366 cc). The mean volume of the $ITV_{MIP}$ not covered by $ITV_{10Phasee}$ was 5.51 cc (6.1%) and the mean volume of $ITV_{10Phases}$ not covered by $ITV_{MIP}$ was 26.33 cc (23.5%) as shown in schematic Figure 2 and Table 3. This suggests that there could be a larger geographical miss of the tumor with $ITV_{MIP}$ in contrast to $ITV_{10Phases.}$

The mean MI (±SD) between $ITV_{MIP}$ and $ITV_{10Phases}$ in all 30 patients was 0.76 ± 0.09 (range 0.57–0.88). The MI for all patients individually is shown in Table 3. MI comparison between two volumes was also done according to tumor size and proximity to equal or high-density structures such as mediastinum, chest wall, and diaphragm [Table 4]. Mean MI for tumors ≤5 cm and >5 cm was 0.75 (±0.08) and 0.77 (±0.08), respectively. Good agreement with mean MI of 77% (±0.06) was seen in tumors that were not close to high-density structures and 73% (±0.09) which were close to high-density structures. The MI was numerically highest in the upper lobe (76%) compared to lower lobe (71%) but was not statistically significant ($P = 0.732$).

DSI was generated only for tumors adjacent to high-density structures. The mean MI of $ITV_{MIP}$ and $ITV_{10Phases}$ for these tumors was 0.73, while the mean DSI of individual phase GTV and $ITV_{10Phases}$ was 0.87. There were only five tumors where inspirtory phase GTV30 has good agreement with $ITV_{10Phases}$, whereas in remaining ten tumors, expiratory phase GTV70 has good agreement with $ITV_{10Phases}$.

The average time required for delineation of $ITV_{MIP}$ was 9 min and $ITV_{10Phases}$ was 96 min. Delineation of $ITV_{10Phases}$

**Table 2: Individual patient characteristics**

| Patient number | Age | Gender | Histology | Laterality | Location | Tumor size (cm) | Proximity |
|---|---|---|---|---|---|---|---|
| 1 | 79 | Male | ADC | Right | Upper | 3 | |
| 2 | 53 | Male | ADC | Right | Upper | 8 | - |
| 3 | 76 | Female | ADC | Right | Lower | 3 | - |
| 4 | 52 | Female | ADC | Right | Upper | 4 | - |
| 5 | 65 | Female | ADC | Left | Upper | 2 | - |
| 6 | 62 | Male | ADC | Right | Upper | 4 | Med |
| 7 | 59 | Male | SCLC | Right | Upper | 5 | CW |
| 8 | 52 | Male | ADC | Left | Lower | 3 | - |
| 9 | 67 | Male | SCLC | Right | Upper | 10 | - |
| 10 | 54 | Male | SCC | Right | Lower | 4 | Med |
| 11 | 65 | Male | SCC | Right | Lower | 4 | - |
| 12 | 45 | Male | SCLC | Left | Upper | 6 | |
| 13 | 63 | Male | SCC | Left | Upper | 5 | - |
| 14 | 51 | Female | ADC | Left | Lower | 11 | CW+diaphragm |
| 15 | 63 | Male | ADC | Left | Upper | 4 | - |
| 16 | 51 | Male | SCC | Right | Middle | 8 | CW |
| 17 | 49 | Male | ADC | Right | Upper | 6 | - |
| 18 | 72 | Male | ADC | Right | Upper | 4 | - |
| 19 | 51 | Male | SCC | Right | Middle | 6 | Med |
| 20 | 70 | Male | SCC | Left | Upper | 2 | Med |
| 21 | 66 | Female | ADC | Right | Middle | 5 | Med |
| 22 | 71 | Male | ADC | Left | Upper | 4 | CW |
| 23 | 59 | Male | SCC | Right | Upper | 7 | CW |
| 24 | 61 | Male | ADC | Right | Upper | 6 | Med |
| 25 | 60 | Male | SCLC | Right | Upper | 5 | CW |
| 26 | 42 | Male | ADC | Left | Upper | 5 | - |
| 27 | 62 | Male | ADC | Right | Upper | 3 | Med |
| 28 | 44 | Male | SCC | Right | Upper | 8 | - |
| 29 | 54 | Male | ADC | Right | Middle | 4 | Middle |
| 30 | 55 | Male | SCC | Right | Lower | 7 | Diaphragm |

ADC: Adenocarcinoma, SCC: Squamous cell carcinoma, SCLC: Small cell lung cancer, CW: Chest wall, Med: Mediastinum

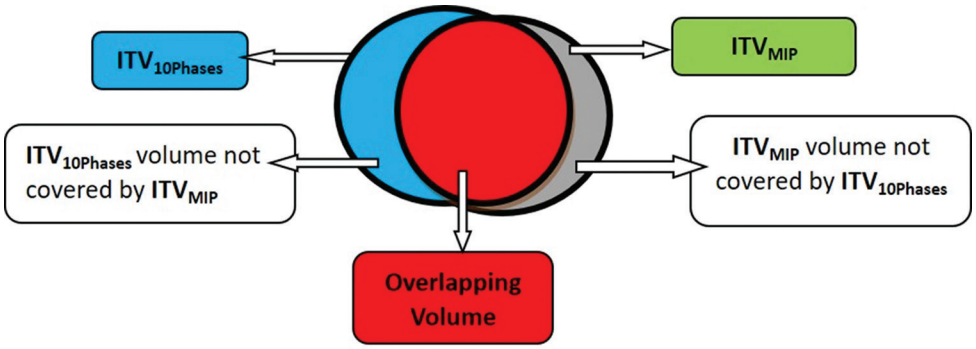


**Figure 2:** Schematic representation of volumes of internal target volume delineated using all 10 phases of four-dimensional compted tomography and internal target volume delineated using maximum intensity projection

was approximately 10–11 times more time-consuming than the time required for $ITV_{MIP}$ delineation.

## Three-dimensional centroid shifts

The COM coordinates and calculated 3D centroid of $ITV_{10Phases}$ and $ITV_{MIP}$ are shown in Supplementary Table 1. Mean of 3D centroid in the superior/inferior, mediolateral, and anterior/posterior axis of $ITV_{10Phases}$ was 0.11 cm, −0.06 cm, and 0.15 cm, respectively, and was 0.11 cm, −0.04 cm, and 0.15 cm for $ITV_{MIP}$, respectively. The mean (±SD) of the 3D centroid shift was −0.01 cm (±0.12) between the $ITV_{MIP}$ and the $ITV_{10Phases}$, suggesting no significant change in the 3D centroid. This indicates that the difference in volume is largely caused by the tumor edges rather than the shift in the COM of two ITVs.

**Table 3: Volumes and matching index of internal target volume delineated using all 10 phases of four-dimensional computed tomography and internal target volume delineated using maximum intensity projection**

| Patient number | $ITV_{10phase}$ (cc) | $ITV_{MIP}$ (cc) | Ratio of $ITV_{10phases}/ITV_{MIP}$ | Matching index | $ITV_{10phases}$ not covered by $ITV_{MIP}$, cc (%) | $ITV_{MIP}$ not covered by $ITV_{10phases}$, cc (%) |
|---|---|---|---|---|---|---|
| 1 | 13.9 | 11 | 1.26 | 0.66 | 4.10 (29.50) | 1.20 (10.91) |
| 2 | 252.5 | 213.7 | 1.18 | 0.78 | 4.10 (14.09) | 3.20 (11.35) |
| 3 | 29.1 | 28.2 | 1.03 | 0.78 | 7.00 (21.28) | 4.10 (13.67) |
| 4 | 32.9 | 30 | 1.09 | 0.71 | 4.10 (17.52) | 0.50 (2.56) |
| 5 | 23.4 | 19.8 | 1.18 | 0.80 | 20.10 (16.80) | 14.30 (12.55) |
| 6 | 119.7 | 113.9 | 1.05 | 0.75 | 19.00 (25.89) | 1.80 (3.20) |
| 7 | 73.4 | 56.2 | 1.30 | 0.73 | 10.60 (15.30) | 2.30 (3.77) |
| 8 | 69.3 | 61 | 1.13 | 0.83 | 44.80 (44.66) | 1.50 (2.63) |
| 9 | 111.1 | 89.7 | 1.23 | 0.76 | 4.60 (13.81) | 1.90 (6.21) |
| 10 | 100.3 | 57 | 1.75 | 0.55 | 26.60 (19.95) | 6.20 (5.49) |
| 11 | 33.3 | 30.6 | 1.08 | 0.82 | 6.90 (18.16) | 4.20 (11.90) |
| 12 | 135.8 | 120.9 | 1.12 | 0.83 | 7.50 (9.80) | 2.50 (3.49) |
| 13 | 133.3 | 112.9 | 1.18 | 0.78 | 14.90 (24.55) | 7.10 (13.42) |
| 14 | 627.4 | 569.5 | 1.10 | 0.86 | 12.20 (17.38) | 4.20 (6.75) |
| 15 | 38 | 35.3 | 1.07 | 0.75 | 11.40 (14.04) | 3.80 (5.16) |
| 16 | 423.5 | 384.4 | 1.10 | 0.82 | 18.60 (23.63) | 0.80 (1.32) |
| 17 | 65.1 | 49.3 | 1.32 | 0.66 | 16.90 (13.98) | 2.60 (2.44) |
| 18 | 76.6 | 71.6 | 1.06 | 0.88 | 14.70 (25.39) | 3.10 (6.70) |
| 19 | 135.5 | 116.8 | 1.16 | 0.76 | 28.90 (37.68) | 3.90 (7.54) |
| 20 | 60.7 | 52.9 | 1.14 | 0.68 | 48.80 (19.37) | 10.0 (4.68) |
| 21 | 70.2 | 62.2 | 1.12 | 0.79 | 24.80 (22.32) | 3.40 (3.79) |
| 22 | 81.2 | 73.6 | 1.10 | 0.83 | 20.50 (15.09) | 5.60 (4.63) |
| 23 | 203.6 | 174.6 | 1.16 | 0.78 | 78.40 (12.50) | 20.50 (3.59) |
| 24 | 182.6 | 165.8 | 1.10 | 0.84 | 59.50 (14.05) | 20.40 (5.31) |
| 25 | 78.7 | 60.9 | 1.29 | 0.76 | 20.00 (30.72) | 4.20 (8.52) |
| 26 | 120.9 | 106.6 | 1.13 | 0.85 | 27.40 (20.22) | 8.70 (7.45) |
| 27 | 57.9 | 46.3 | 1.25 | 0.71 | 38.29 (18.81) | 9.30 (5.33) |
| 28 | 455.2 | 370.5 | 1.22 | 0.80 | 23.70 (12.98) | 6.90 (4.16) |
| 29 | 76.7 | 51.7 | 1.48 | 0.61 | 89.00 (19.55) | 4.30 (1.16) |
| 30 | 104.8 | 64.9 | 1.61 | 0.57 | 82.60 (57.04) | 2.70 (4.16) |
| Mean±SD | 134.2±139.1 | 113.4±124.2 | 1.19±0.16 | 0.75±0.9 | 26.33±23.65 (23.53±10.16) | 5.51±5.07 (6.12±3.61) |
| Median | 79.95 | 63.55 | 1.15 | 0.78 | 19.50 (19.09) | 4 (5.23) |

$ITV_{MIP}$: Internal target volume delineated using maximum intensity projection, $ITV_{10phases}$: Internal target volume delineated using all 10 phases of four-dimensional CT, SD: standard deviation, CT: Computed tomography

**Table 4: Matching index according to tumor proximity to high-density structures and tumor size**

| | Tumours in close proximity ($n=15$) | Tumours not in close proximity ($n=15$) | Tumor size ≤5 cm ($n=19$) | Tumor size >5 cm ($n=11$) |
|---|---|---|---|---|
| Mean±SD | 0.73±0.09 | 0.77±0.06 | 0.75±0.08 | 0.77±0.08 |
| Median | 0.76 | 0.78 | 0.76 | 0.78 |

SD: Standard deviation

## Discussion

ITV delineation using the MIP dataset of 4D-CT scan is the commonly used approach for motion encompassment of primary tumor in RT planning of early and locally advanced LC. ITV using MIP and all 10 phases have been compared in few studies of LC. However, to our knowledge, our study is the largest to compare these two techniques (MIP and all 10 phases) in consecutive early and locally advanced NSCLC. Our study results demonstrated that $ITV_{10Phases}$ volume is significantly larger ($P < 0.001$) as compared to $ITV_{MIP}$ volume. This finding concurs with the existing literature.[9-11] The mean volume of the $ITV_{10Phases}$ not covered by the $ITV_{MIP}$ was 23.5%, in contrast to $ITV_{MIP}$ not covered by $ITV_{10Phases}$ was 6.1%. This suggests that the use of $ITV_{MIP}$ alone could lead to a larger geographical miss of the tumor, resulting in tumors under dosage and inferior local control.

Muirhead *et al*., in a similar study of 14 patients of advanced-stage LC also, compared the same two techniques for ITV generation and reported that $ITV_{MIP}$ is significantly smaller than $ITV_{10phases}$ ($P < 0.001$).[10] The mean ratio of $ITV_{10phases}$ to $ITV_{MIP}$ was 1.23 compared to 1.19 in our study. The mean percentage of $ITV_{10phases}$ not covered by $ITV_{MIP}$ was 18.5%, similar to the findings of our study (23.5%). The authors concluded that for stage II and III tumors, MIP is not a reliable clinical tool for ITV generation. The only difference between these two studies is that Muirhead *et al*. also included nodal volume in ITV. Underberg *et al*. analyzed 4D-CT data from 12 patients of stage I LC and generated ITVs from all 10 phases and MIP.[9] The $ITV_{10Phases}$ volume was larger compared to $ITV_{MIP}$ volume and the average ratio between $ITV_{10Phases}$ and $ITV_{MIP}$ was $1.07 \pm 0.05$ compared to $1.17 \pm 0.13$ in our study. This difference could be explained by more advanced-stage tumors in our study. In smaller tumors, there would be a sharp contrast between high-density tumors and lower-density lung parenchyma, and hence, delineation uncertainty is less compared to larger tumors. Underberg *et al*. concluded that ITV generation using MIP is a reliable technique from a 4D-CT data set for stage I lung cancer. However, this ratio in our study is $1.19 \pm 0.17$ for smaller tumors less than 5 cm and the possible explanation could be as more tumors were close to adjacent structures [Table 2]. Ezhil *et al*. compared four techniques of internal gross target volume (iGTV) delineation, namely $iGTV_{10phases}$, $iGTV_{2Phases}$, $iGTV_{MIP}$, and $iGTV_{MIP\text{-}Modified}$ visually in each phase in 17 stage I and 10 stage III consecutive patients of LC.[11] Similar to our results, $iGTV_{MIP}$ was consistently smaller than $iGTV_{10Phases}$ in all patients. MI was 0.8 and 0.86 in stage I and III tumors, respectively, compared to 0.75 and 0.77 in this study. The underestimation of $iGTV_{10Phase}$ by $iGTV_{MIP}$ was on an average 17.3% in stage I and 12.1% in stage III tumors compared to 22% and 20.6% in tumor ≤5 and >5 cm, respectively, in our study.

Precise tumor delineation of T1 and T2 tumor is comparatively easy, where higher density tumor tissue moves within the much lower density of the lung allowing good contrast between tumor edges and normal lung parenchyma. In contrast, the probability of larger tumors to be adjacent to equal or high-density structures such as mediastinum, chest wall, and diaphragm is higher. MI for tumor close to these structures was 0.73 and tumors away from these structures was better at 0.77. Ezhil *et al*. also reported a similar finding of worse MI for tumors close to high-density structures in their study.[11] However, MI was not different according to tumor size in our study (MI = 0.75 for ≤5 cm and 0.77 for >5 cm), probably because a considerable number of smaller tumors ($n = 9$) were close to these structures. This suggests that tumor size does not affect the MI unless the tumor is close to the mediastinum, chest wall, and diaphragm. For tumors located in the periphery, any of the two ITV delineation approaches is acceptable; however, for tumors adjacent to high-density structures, $ITV_{MIP}$ alone may not be sufficient and requires additional verification of tumor volume.

A similar volume of $ITV_{10Phases}$ and $ITV_{MIP}$ does not necessarily mean that the two ITVs would also be identical, and their centroid could be different resulting in a systematic error. This shift between the centroid of two volumes could be due to many reasons namely hysteresis, motion artifacts in MIP reconstruction, or delineation error. The mean of 3D centroid shift between two volumes in our study was 0.01 cm, suggesting no significant change in the 3D centroid. This indicates that the difference in volume is largely caused due to difficulties in demarcating tumor edges rather than the shift in the COM of two ITVs. A difference of 0.01 cm of 3D centroid shift is quite small and will not have any clinical impact in routine clinical practice. The mean centroid shift between ITVMIP and ITV 10 phases was reported as 0.34 cm by Muirhead et al and 0.04 cm by Underberg et al. These findings were similar to that of our study (0.01 cm).[9,10] A shift of 0.34 cm in Muirhead *et al*'s study could be due to the inclusion of nodal volume as delineating nodes are challenging on MIP because of blurred distinctions between nodal and normal tissue.

The advantage of MIP is that it gives a single 3D-CT dataset that encompasses an entire range of tumor motion and ITV delineation can be done directly in a time-efficient manner. However, there are certain limitations also with MIP. First, it can have postprocessing artifacts if the patient's breathing is not regular during 4D-CT acquisition. Second, its utility is limited in mobile tumors adjacent to equal or higher density structures as shown by many studies. Third, tumor smearing at the edges and nonvisualization of tumor spiculations, especially in smaller tumors treated with stereotactic body RT with high-dose gradient. Fourth, MIP represents a higher density dataset overall than actual density and hence cannot be used for planning. Alternatively, FB-CT, end-expiration phase of 4D-CT, or AveIP[16] can be used for treatment planning. Finally, nodal tissue and organs at risk delineation on MIP are also under question and clinical research.

The average time required for delineation of $ITV_{MIP}$ was 9 min while $ITV_{10Phases}$ was 96 min. Delineation of tumor in all phases required additional contouring time from the radiation oncologist, so it may not be practical to adopt the $ITV_{10Phases}$ approach in routine clinical practice for all stage patients, especially in large-volume centers. Alternate techniques for ITV delineation using AveIP dataset, two extreme phases of respiration, time-weighted mean tumor position, and 4D magnetic resonance imaging (4D-MRI)[17] are also studied in the literature to circumvent the fallacies of MIP and time efficient in comparison to contouring in all 10 phases of 4D-CT.[9,11,13,14] A study by Bradley *et al*. compared MIP and AveIP datasets in 20 inoperable peripheral stages I lung tumors.[13] The authors concluded that MIP is superior to AveIP to depict tumor motion. However, as no comparison to the $ITV_{10Phases}$ was done, so whether the actual tumor is represented accurately by the $ITV_{MIP}$ was unclear. Yeo *et al*. compared $ITV_{2Phases}$ (0 and 50) and $ITV_{4Phase}$ (0, 50, 20, and 70) with $ITV_{10Phases}$ in 15 patients and showed that $ITV_{10phases}$ was significantly larger than both and MI of $ITV_{4Phase}$ was

significantly higher than $ITV_{2Phases}$.[14] Ezhil *et al*. also showed that $ITV_{2Phase}$ was significantly inferior to $ITV_{10Phases}$ as $ITV_{MIP}$, but $ITV_{MIP\text{-}Modified}$ matched closely with $ITV_{10Phases}$. The authors described $ITV_{MIP\text{-}Modified}$ as contouring on MIP with visual verification in every phase of the respiratory cycle. This is what we do currently in larger tumors close to high-density structures at our institution. In our study, we also evaluated DSI to determine which individual phase GTV correlated with $ITV_{10Phases}$ to reduce the time required for delineation of primary tumor in all phases. We observed that GTV30 and GTV70 closely correlated and could be used for delineation instead of all phases. However, this needs to be studied in larger patient cohort for validation. The disadvantage of using two extreme phases of respiration is that they do not take into account tumor hysteresis, mediolateral, and anteroposterior movement completely. Questions remain as to how many phases we should consider optimal for delineating ITV.

The advantage of our study is that single RO contoured the target volume which also explains the larger volume of $ITV_{10phases}$ in all patients than $ITV_{MIP}$. It also excludes interobserver variation and resultant bias. We incorporated all stages of LC patients. It would be pertinent to discuss the limitations of this study. First, one more RO for contouring volumes in the same all patients would have further strengthened our results. Second, nodal volumes were not contoured on both datasets as we believe lymph nodes cannot be accurately delineated on a MIP dataset due to the blurring of nodal tissue and mediastinal soft tissue. Third, ITV generation using AveIP or time-weighted mean tumor position could have also been compared with $ITV_{MIP}$. Fourth, a dosimetric analysis was not done between the two modalities of ITV delineation to see if there is any dosimetric difference in target volume or organ at risk parameters.

To date, there is no acceptable standard technique recommended in the literature for ITV delineation using 4D-CT. Each technique has its advantages and disadvantages compared to others. Each institute has to standardize their technique for ITV delineation based upon their own experience, facilities available, and patient throughput. In conclusion, we suggest for continued use of $ITV_{MIP}$ for smaller tumors where it moves within well contrast lung parenchyma and exercise caution in tumors close to mediastinum, chest wall, and diaphragm. Additional visual verification in each phase or extreme phases of respiration for accurate estimation of tumor motion could be reasonable options, however, requires further clinical research.

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## Conflicts of interest

There are no conflicts of interest.

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**Supplementary Table 1: 3D centroid and 3D centroid shift between ITV10Phases & ITVMIP**

| Patients No | $ITV_{10Phases}$ | | | 3D Centroid $ITV_{10Phases}$ (cm) | $ITV_{MIP}$ | | | 3D Centroid $ITV_{MIP}$ (cm) | 3D Centroid Shift (cm) |
|---|---|---|---|---|---|---|---|---|---|
| | x | y | z | | x | y | z | | |
| 1 | 5.5 | -17.6 | 5.2 | 19.16 | 5.4 | -17.7 | 5.2 | 19.22 | -0.06 |
| 2 | 5.6 | -13.8 | 4.1 | 15.45 | 5.6 | -13.7 | 4.3 | 15.41 | 0.04 |
| 3 | 6.5 | -12.6 | -1.1 | 14.22 | 6.5 | -12.5 | -1.1 | 14.13 | 0.09 |
| 4 | 4.5 | -5.7 | -1.7 | 7.46 | 4.5 | -5.7 | -1.7 | 7.46 | 0.00 |
| 5 | -5.0 | -17.1 | -4.7 | 18.43 | -5.0 | -17.1 | -4.7 | 18.43 | 0.00 |
| 6 | 5.4 | -6.3 | 1.8 | 8.49 | 5.5 | -5.9 | 1.9 | 8.29 | 0.20 |
| 7 | 8.0 | -8.9 | 6.1 | 13.43 | 8.1 | -8.4 | 6.2 | 13.21 | 0.22 |
| 8 | -6.2 | -2.3 | 7.1 | 9.70 | -6.2 | -2.4 | 7.3 | 9.87 | -0.17 |
| 9 | 6.8 | -9.7 | 0.7 | 11.87 | 7.0 | -9.8 | 0.6 | 12.06 | -0.19 |
| 10 | 4.1 | -8.7 | 4.4 | 10.58 | 3.9 | -8.3 | 4.4 | 10.17 | 0.40 |
| 11 | 8.1 | -4.5 | 6.2 | 11.15 | 8.1 | -4.5 | 6.1 | 11.09 | 0.06 |
| 12 | -8.6 | -7.1 | 3.3 | 11.63 | -8.6 | -7.1 | 3.3 | 11.63 | 0.00 |
| 13 | -5.5 | 3.8 | -10.3 | 12.28 | -5.4 | 3.8 | -10.3 | 12.23 | 0.04 |
| 14 | -5.4 | 1.2 | 1.0 | 5.62 | -5.5 | 1.2 | 1.0 | 5.72 | -0.10 |
| 15 | -6.5 | 0.5 | -7.3 | 9.79 | -6.5 | 0.4 | -7.3 | 9.78 | 0.00 |
| 16 | 7.6 | 3.3 | -0.9 | 8.33 | 7.8 | 3.4 | -0.9 | 8.56 | -0.22 |
| 17 | 5.5 | -1.4 | -8.9 | 10.56 | 5.5 | -1.3 | -8.8 | 10.46 | 0.10 |
| 18 | 4.9 | 5.2 | -11.7 | 13.71 | 4.9 | 5.2 | -11.8 | 13.79 | -0.09 |
| 19 | 5.0 | -4.0 | -3.3 | 7.20 | 5.2 | -4.0 | -3.2 | 7.30 | -0.10 |
| 20 | -2.5 | 0.6 | -10.7 | 11.00 | -2.4 | 0.6 | -10.8 | 11.08 | -0.08 |
| 21 | 5.2 | -3.1 | -4.1 | 7.31 | 5.1 | -3.4 | -4.1 | 7.37 | -0.06 |
| 22 | -4.5 | -9.6 | -1.9 | 10.77 | -4.5 | -9.6 | -1.9 | 10.77 | 0.00 |
| 23 | -0.2 | -15.7 | 7.5 | 17.40 | 00 | -15.9 | 7.8 | 17.71 | -0.31 |
| 24 | 5.2 | -10.5 | 4.3 | 12.48 | 5.2 | -10.5 | 4.4 | 12.52 | -0.03 |
| 25 | 5.0 | -15.7 | 2.1 | 16.61 | 5.0 | -15.8 | 2.0 | 16.69 | -0.08 |
| 26 | -7.1 | -10.1 | 1.5 | 12.44 | -7.1 | -10.2 | 1.5 | 12.52 | -0.08 |
| 27 | 3.7 | -11.3 | 1.1 | 11.94 | 3.9 | -11.4 | 1.1 | 12.10 | -0.16 |
| 28 | 5.4 | -18.7 | 3.8 | 19.83 | 5.4 | -18.4 | 3.7 | 19.53 | 0.30 |
| 29 | 4.1 | -4.6 | 2.6 | 6.69 | 4.2 | -4.8 | 2.7 | 6.93 | -0.24 |
| 30 | 4.4 | -3.6 | 5.1 | 7.64 | 3.8 | -4.0 | 4.9 | 7.38 | 0.26 |
| Mean ±SD | 0.11 | -0.06 | 0.15 | 11.77±3.81 | 0.11 | -0.04 | 0.15 | 11.78±3.80 | -0.01 |

$ITV_{MIP}$ – Internal target volume delineated using maximum intensity projection, $ITV_{10Phases}$ – Internal target volume delineated using all 10 phases of four-dimensional CT, SD = standard deviation