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Optimizing the methodology for calculating the 4DCT derived internal target volume in stereotactic radiotherapy for Non-Small Cell Lung Cancer (NSCLC)

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ABSTRACT

This study aimed to investigate efficient methods for determining the Internal Target Volume (ITV) using Four-Dimensional Computed Tomography (4DCT) images in Stereotactic Body Radiotherapy (SBRT) for patients with early-stage Non-Small Cell Lung Cancer (NSCLC). The study involved 55 patients who underwent SBRT for stage I NSCLC, with their 4D CT images analyzed to determine the ITVs. The Matching Index (MI) for ITV4Phases and ITV2Phases was calculated as the ratio of these volumes to ITV10Phases. Significant differences were observed among the various ITVs, with distinct orders for ITV10Phases, ITV4Phases, and ITV2Phases. Notably, the MI for ITV4Phases was significantly higher than that for ITV2Phases. Additionally, there was an inverse relationship between the MI of ITV4Phases and the Total Motion Index (TMI) (r=0.0067, p=0.5507). In a subgroup with low TMI, ITV4Phases did not show a significant difference from ITV10Phases (p=0.8003), and its MI was significantly higher than that of ITV2Phases.Therefore, ITV4Phases emerges as a potentially efficient alternative to the optimal ITV10Phases in SBRT for early-stage NSCLC, especially in cases with reduced tumor motion.

Keywords: Non-Small Cell Lung Cancer (NSCLC), stereotactic body radiotherapy, internal target volume, matching index and tumor motion index

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INTRODUCTION

Stereotactic Body Radiotherapy (SBRT) has emerged as a highly effective treatment modality for Non-Small Cell Lung Cancer (NSCLC), particularly in early-stage disease where precise targeting is paramount. One of the critical challenges in SBRT is accounting for the tumor motion caused by respiration, which can significantly impact the accuracy of radiation delivery. To address this, Four-Dimensional Computed Tomography (4DCT) is employed to capture the temporal variations in tumor position, facilitating a more comprehensive understanding of its motion [1-9]. The Internal Target Volume (ITV) concept is pivotal in SBRT for NSCLC, as it encompasses the entire spatial extent of the tumor throughout the respiratory cycle. Accurately defining the ITV is essential to ensure the tumor receives the prescribed dose while minimizing exposure to surrounding healthy tissues. Traditional methods for determining the ITV often involve manual contouring of the tumor on multiple respiratory phases, which can be labor-intensive and subject to variability [10-16]. Recent advancements in imaging and computational techniques offer new opportunities to optimize the calculation of ITV. By integrating sophisticated algorithms and automation into the 4DCT analysis, it is possible to enhance the precision and reproducibility of ITV delineation. This optimization not only improves the efficacy of SBRT but also reduces the workload on clinicians and enhances patient outcomes [17-23].

In lung SBRT, technical aspects such as image guidance and motion management are crucial due to tumor movement caused by respiration. Four-Dimensional Computed Tomography (4DCT) plays a key role by allowing for precise tumor localization through the correlation of respiratory motion with CT imaging [10-16]. This technique provides detailed information about the tumor's size, shape, and position throughout the respiratory cycle. To address tumor motion, the concept of an Internal Target Volume (ITV) was introduced. The ITV encompasses the Clinical Target Volume (CTV) along with an additional margin to account for uncertainties due to tumor motion. Ideally, this involves contouring the CTV on each of the 10 respiratory phase images obtained through 4D CT. However, this method poses practical challenges due to the increased workload for radiation oncologists [17-23].

This study aims to explore and refine methodologies for calculating the ITV derived from 4DCT in the context of NSCLC treated with SBRT. By leveraging advanced computational tools and

rigorous validation techniques, we seek to establish a more accurate, efficient, and consistent approach to defining the ITV, thereby contributing to the overall improvement of SBRT practices for lung cancer patients. This study aimed to evaluate the feasibility of determining ITV based on either two phases compared to the reference method of using all 10Phases to define the ITV [24-29].

MATERIALS AND METHODS

A retrospective analysis was performed on a cohort of fifty-five patients diagnosed with stage I Non-Small Cell Lung Cancer (NSCLC). These patients underwent 4 Dimensional Computed Tomography (4DCT) simulation for treatment planning and received curative Stereotactic Body Radiotherapy (SBRT) from 2019 to 2023. The inclusion criteria for SBRT adhered to the UK Stereotactic Ablative Body Radiation Therapy (SABR) consortium guidelines and included histologically confirmed NSCLC, clinical stage T1-2N0M0, a tumor diameter of less than 5 cm, and a performance status score of 2 or less. The median age of the patients was 77 years, with an age range of 68 years to 86 years, and 30 patients (71.4%) were male. SBRT was specifically offered to patients who were either medically unsuitable for surgery or who opted out of surgical intervention. An additional requirement was that the treated tumor had to be located at least 2 cm away from the proximal bronchial tree in all directions.

ITV determination

During the 4DCT simulation, patients were positioned in a supine position with their arms elevated above their heads. This setup utilized an All-in-One (AIO) board equipped with a headrest and shoulder support. The simulation employed a Real-time Position Management (RPM) system alongside a General Electric Company (GE) light speed extra 16 slice CT scanner, which provided images with a slice thickness of 0.25 cm. Not all patients received intravenous contrast for the scan. The data collection spanned a complete respiratory cycle, resulting in a series of 10 CT images, each representing 10% of the respiratory cycle. The Gross Tumor Volume (GTV) was defined on each CT image using the 'lung window' setting, without any expansion to account for microscopic disease. Therefore, the Clinical Target Volume (CTV) was the same as the gross tumor volume.

Three methods were utilized to define Internal Target Volumes (ITVs)

ITV10Phases:

GTVs were contoured on each of the 10 respiratory phases within the 4D CT dataset. These individual GTVs were then combined to form ITV10Phases.

ITV4Phases:

GTVs from four specific respiratory phases-0% (peak inspiration), 20% (mid-expiration), 50% (peak expiration), and 70% (mid-inspiration)-were combined to create ITV4Phases.

ITV2Phases:

This method involved combining GTVs from only two extreme respiratory phases, specifically 0% (peak inspiration) and 50% (peak expiration), to generate ITV2Phases.

PTV determination

PTV is an essential element in radiation therapy planning. It encompasses the GTV and the CTV, accounting for potential variations in the patient's positioning and internal organ motion. The purpose of PTV is to ensure that the prescribed dose of radiation covers the tumor despite these uncertainties. By incorporating margins around the GTV and CTV, PTV allows for more accurate targeting, reducing the risk of underdoing the tumor or overdosing healthy tissue. There will be no expansion of the CTV to accommodate microscopic disease, so we do not need to consider the CTV margin volume.

RESULTS

The study evaluated ITV4Phases and ITV2Phases in comparison to ITV10Phases using the Motion Index (MI). Since both ITV4Phases and ITV2Phases are entirely encompassed by ITV10Phases, the MI was calculated as the ratio of ITV4Phases and ITV2Phases to ITV10Phases, respectively. An MI value of 1 indicates that the volumes are identical. Statistical analysis was conducted using SPSS software version 14.0. Depending on the data characteristics, paired or independent-sample t-tests were utilized for intergroup comparisons. The Spearman correlation coefficient was employed to determine the correlation between TMI and MI. A p-value of less than 0.05 was considered statistically significant for all analyses, with the reported p-values being two-tailed.

Table 1 presents the values of ITV, PTV, TMI, and MI for all patients. Among the cohort, 24 patients had tumors located in the upper lobe, 9 in the middle lobe, and 22 in the lower lobe. Although tumors situated in the lower lobe exhibited a slightly higher TMI compared to those in the mid-upper lobes, this difference was not statistically significant. Similarly, tumors with smaller sizes tended to have higher TMI values, albeit without statistical significance.

This represents the volume of a tumor as observed across different phases of respiration or other physiological variations. ITV4Phase and ITV2Phase likely refer to ITV calculated from imaging across four phases and two phases respectively. This is an expansion of the ITV to account for uncertainties in treatment delivery, such as patient setup errors and organ motion. PTV4Phase and PTV2Phase would be the planning target volumes corresponding to the ITV volumes from four phases and two phases shown in figures 1-3.

Tab. 1. The Internal Target Volume (ITV), Planning Target Volume (PTV), tumor motion index, and matching index across all patients

	Mean	SD	Range
ITV10Phases	14.25	12.58	54.7-0.7
ITV4Phases	18.52	15.61	65.1-1.1
ITV2Phases	16.89	14.48	63.7-1.0
PTV10Phases	37.74	26.1.0	115.8-5.6
PTV4Phases	44.27	29.92	130.9-7.1
PTV2Phases	41.64	28.36	129.6-2

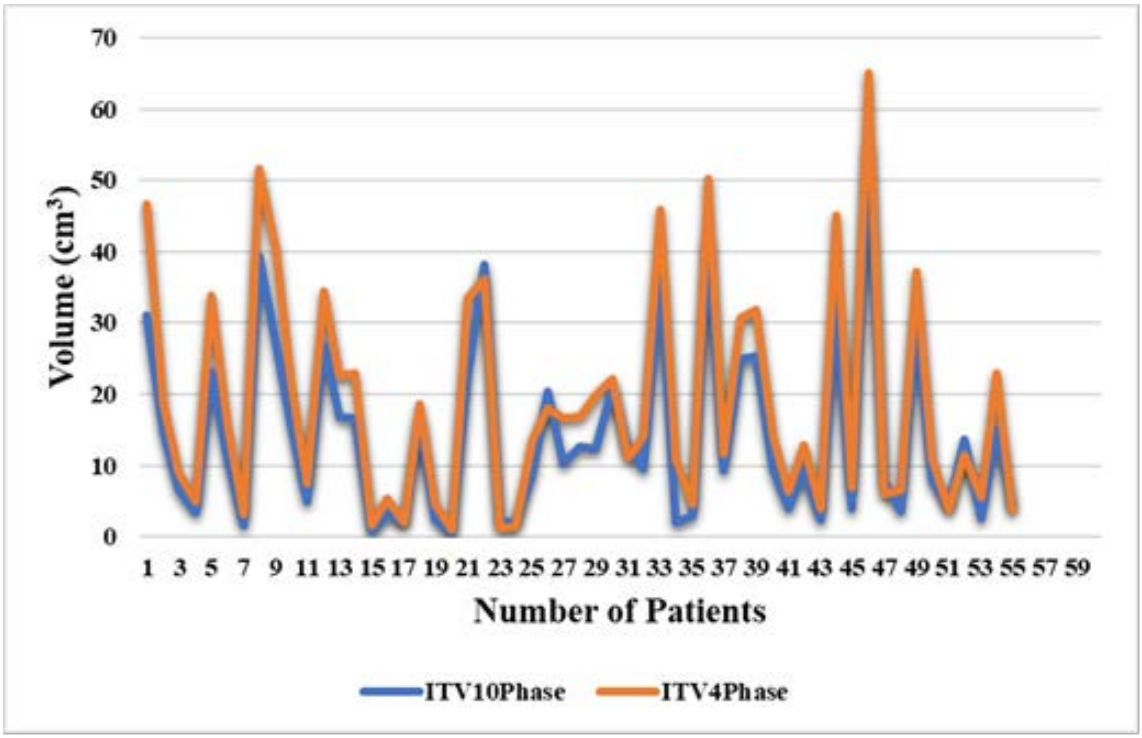

Fig. 1. Matching index of ITV10Phases *vs.* ITV4Phases

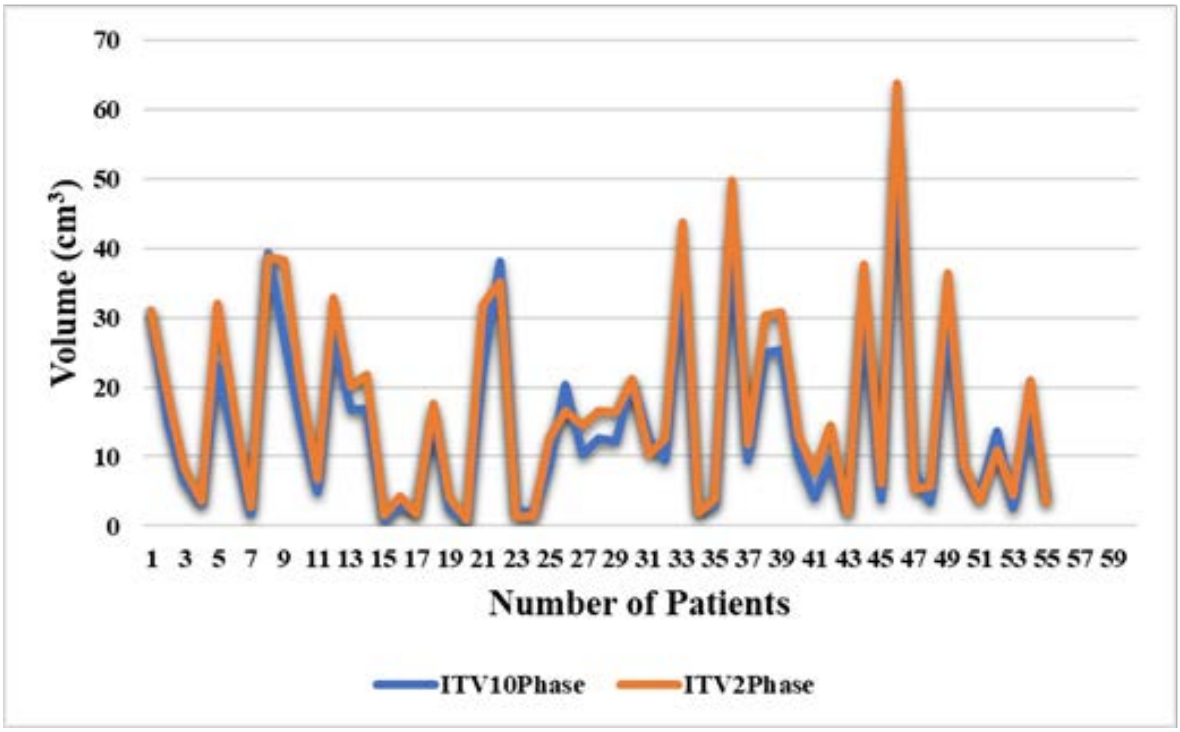

Fig. 2. Matching index of ITV10Phases *vs.* ITV2Phases

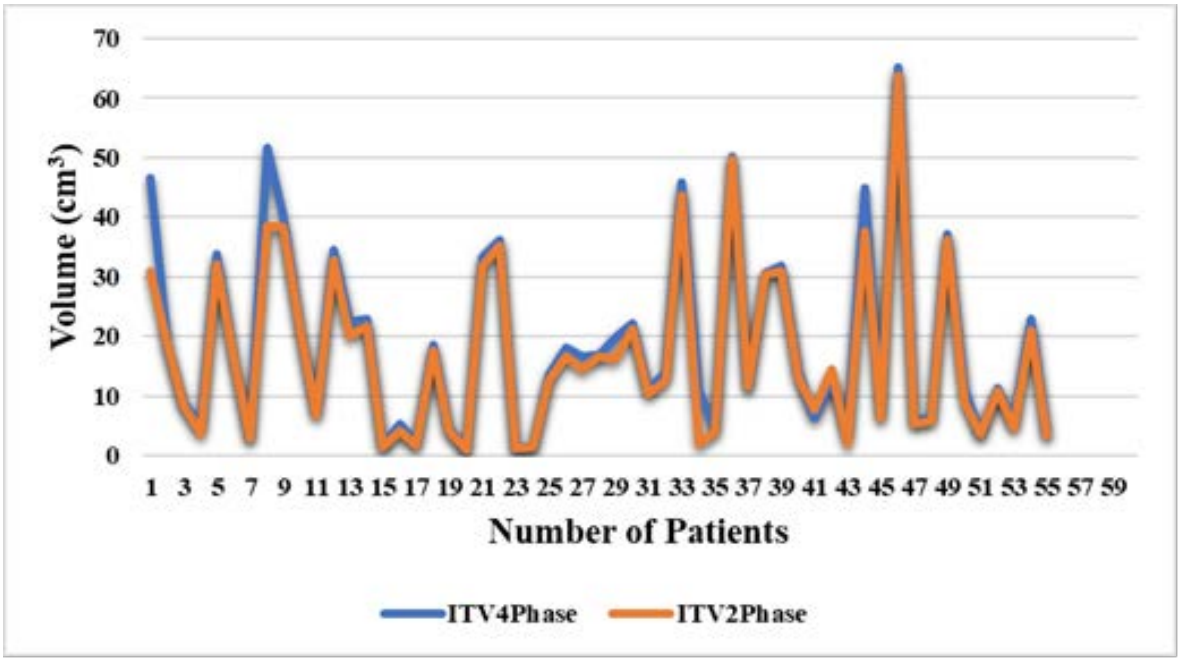

Fig. 3. Matching index ITV4Phases *vs.* ITV2Phases

This comparison would assess how consistent the observed tumor volumes are across four phases of imaging compared to just two phases. A higher matching index would suggest greater consistency across all phases, indicating a more stable tumor volume throughout the respiratory cycle or other variations. This comparison would evaluate how the planned treatment volumes (including margins for setup errors and organ motion) differ when based on ITV from four phases versus two phases. A higher matching index here would indicate that the planned treatment volumes are more consistent across different phases of imaging, which is crucial for accurate and effective radiation therapy delivery. In both cases, a higher matching index would generally be desirable as it suggests more uniformity and consistency in tumor delineation and treatment planning, which can lead to better treatment outcomes. The volumes for ITV10Phase, ITV4Phase and ITV2Phase were 14.25 cm^3 ± 12.58 cm^3, 18.52 cm^3 ± 15.61 cm^3, and 16.89 cm^3 ± 14.48.3 cm^3, respectively. Significant differences were observed between each ITV:

- ITV10Phases *vs.* ITV4Phase, p=0.8003, R^2=0.0012;
- ITV10Phase *vs.* ITV2Phase, p=0.8003, R^2=0.0012;
- ITV4Phase *vs.* ITV2Phase, p=0.5507, R^2=0.0067.

The MI of ITV4Phase was significantly higher than that of ITV-2Phase. Similarly, the MI of PTV4Phase was significantly higher than that of PTV2Phase in figures 4-6. The volumes for PTV-10Phase, PTV4Phase, and PTV2Phase were 37.74 cm^3 ± 26.10 cm^3, 44.27 cm^3 ± 29.92 cm^3, and 41.64 cm^3 ± 28.36 cm^3, respectively. Significant differences were observed between each ITV:

- PTV10Phases *vs.* PTV4Phases, p=0.8374, R^2=0.0011;
- PTV10Phases *vs.* PTV2Phases, p=0.8374, R^2=0.0011; and
- PTV4Phases *vs.* PTV2Phases, p=0.5957, R^2=0.0053

Upon grouping patients based on a median TMI value of 1.58, significant differences in ITV4Phases (18.52 cm^3 ± 15.61 cm^3) compared to ITV10Phases (14.25 cm^3 ± 12.58 cm^3) were observed in patients with high TMI (n=55, p=0.8003). Conversely, in patients with low TMI no statistically significant difference was noted between ITV4Phases (18.52 cm^3 ± 15.61 cm^3) and ITV-10Phases (14.25 cm^3 ± 12.58 cm^3) (p=0.8003). Notably, in the low TMI group, the difference between PTV10Phases (14.25 cm^3 ± 12.58 cm^3) and PTV4Phases (44.27 cm^3 ± 29.92 cm^3) was further reduced (p = 0.5957). Irrespective of TMI, both MI values of ITV4Phases and PTV4Phases remained significantly higher compared to their respective ITV2Phases and PTV2Phases counterparts.

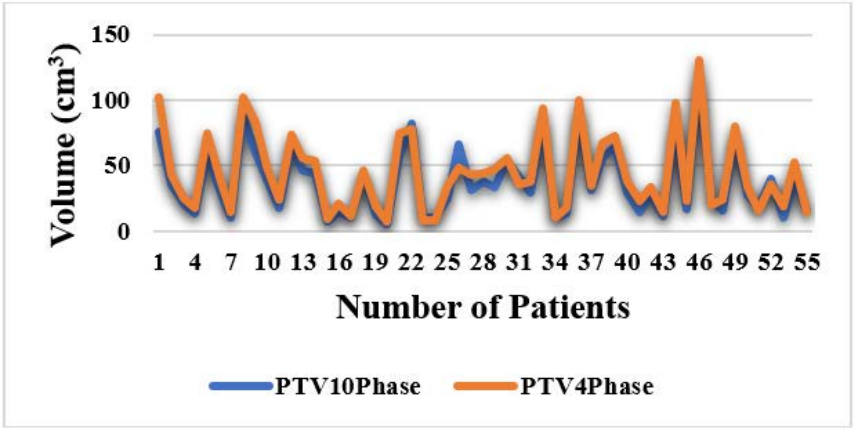

Fig. 4. Matching index of PTV10Phases *vs.* PTV4Phases

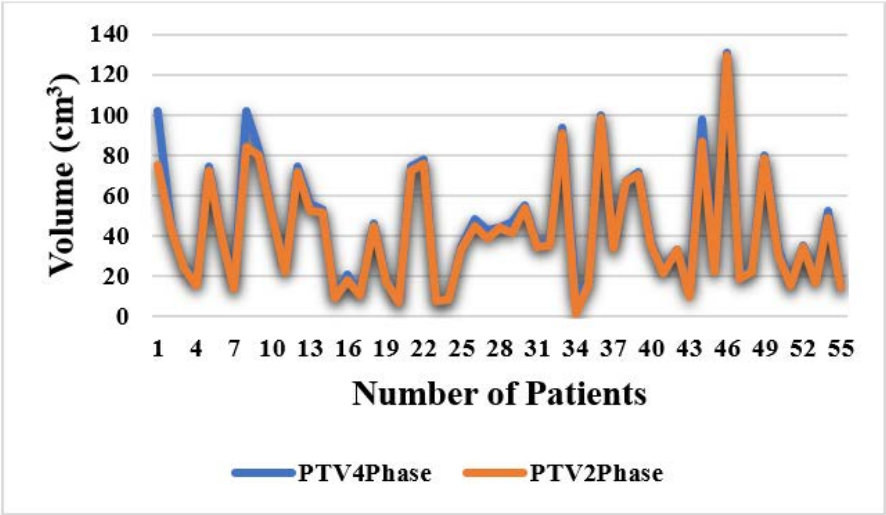

Fig. 5. Matching index PTV10Phases *vs.* PTV2Phases

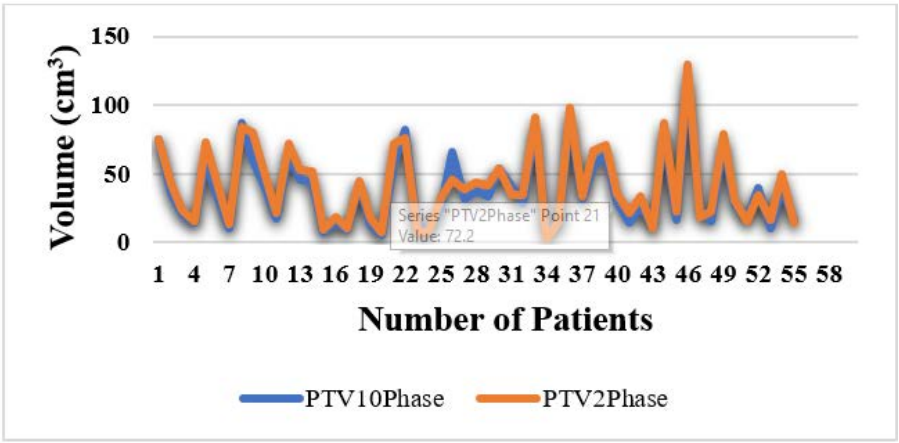

Fig. 6. Matching index PTV4Phases *vs.* PTV2Phases

Figure 7 presented boxplot showing distribution of 4a for ITV-10Phases, ITV4Phases, and ITV2Phases and 4b for PTV10Phases, PTV4Phases, and PTV2Phases. Compare the medians of ITV10Phases, ITV4Phases, and ITV2Phases to see how central tendencies change with different phases. Similarly, compare the medians of PTV10Phases, PTV4Phases, and PTV2Phases shown in figures 7 and 8. Then, compare ITV and PTV datasets for each phase to observe differences between the two types. Look at the IQR and overall range for each phase and type to see how variability changes. The Median Values Suppose the median of ITV10Phases is higher than that of ITV4Phases and ITV2Phases, suggesting that the central tendency decreases as phases decrease. Conversely, PTV datasets might show a different trend, such as a relatively stable median across phases. The IQR and Overall Range: If ITV10Phases has the largest IQR and range, it indicates that the data in the 10Phases are more spread out and variable compared to the 4Phases and 2Phases. If PTV datasets show a smaller IQR, this suggests less variability within each phase. If ITV2Phases shows a skewed distribution with longer whiskers on the upper side, it might indicate the presence of high outliers or skewness toward higher values. If PTV4Phases has a symmetrical box plot, it suggests a more even distribution of values. Suppose PTV10Phases has several outliers compared to other datasets. This could mean there are more extreme values or variability in the PTV data when considering 10Phases.

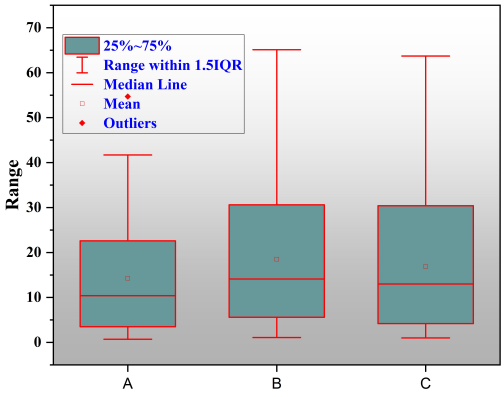

Fig. 7. 7A. Tumor motion index ITV2Phases **7B.** ITV4Phases **7C.** ITV10Phases

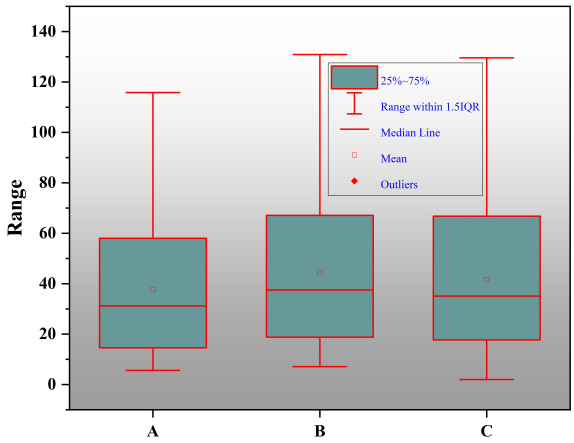

Fig. 8. 8A. Tumor motion index PTV2Phases **8B.** PTV4Phases **8C.** PTV10Phases

DISCUSSION

Stereotactic Body Radiotherapy (SBRT) has emerged as an effective and safe treatment option for patients with medically inoperable early-stage Non-Small Cell Lung Cancer (NSCLC). Recent research has demonstrated promising clinical outcomes, including favorable local tumor control and minimal toxicity. However, many initial experiences with lung SBRT used standard population based margins for internal target motion, without specifically delineating tumor contours that encompass the entire trajectory of the breathing cycle. This approach can lead to overestimation or underestimation of the required margins due to variability in individual breathing characteristics. Overestimation increases the exposure of healthy tissue to high radiation doses, while underestimation can result in missed targets and reduced tumor control. Tumor size, location, and pulmonary function tests have proven to be unreliable predictors of lung tumor motion, a finding consistent with our study, where no correlation was found between tumor size or location and the extent of Tumor Motion Index (TMI). There are three main methods for implementing SBRT using 4D CT scans: the Internal Target Volume (ITV) method using static fields, the gating method that synchronizes tumor location with beam timing, and tracking methods that continuously follow the tumor during therapy. The ITV approach is the most commonly used and straightforward technique, allowing for the determination of patient-specific ITVs, ensuring adequate tumor coverage while minimizing radiation to healthy tissues. However, contouring across 10 respiratory phases to define ITV is labor-intensive for routine clinical practice. To reduce this burden, post-processing tools such as Maximum Intensity Projection (MIP) images are sometimes used. Nonetheless, studies have shown that ITVs based on MIP images tend to underestimate ITVs compared to the 10 phase method, and caution is advised due to potential uncertainties. Similarly, our study found significant underestimation of ITV2Phases compared to ITV10Phases, even in patients with low TMI. In contrast, our investigation focused on ITV4Phases, which includes two intermediate respiratory phases (mid-inspiration and mid-expiration) along with the two extreme phases. This method significantly improved the Matching Index (MI) compared to ITV2Phases and eliminated the significant. Underestimation of ITV observed with ITV2Phases in patients with low TMI. Including intermediate respiratory phases helps address uncertainties related to lung motion, such as nonlinearity and hysteresis during free breathing. Our study also found a significant inverse correlation between TMI and the MI of ITV-4Phases, supporting previous findings.

CONCLUSION

In conclusion, defining the Internal Target Volume (ITV) based on four respiratory phases, including two intermediate phases, provides a practical alternative to the comprehensive ITV10Phases approach. For patients with a low Total Motion Index (TMI), this method did not significantly underestimate the tumor volume and significantly reduced the workload. Therefore, ITV4Phases can be an efficient alternative for Stereotactic Body Radiotherapy (SBRT) in early-stage Non-Small Cell Lung Cancer (NSCLC) patients, particularly when the ITV10Phases method is impractical for routine clinical application. By examining and comparing the box plots of ITV10Phases, ITV4Phases, and ITV2Phases along with the corresponding planning target volumes (PTV10Phases, PTV4Phases and PTV2Phases), we can draw meaningful conclusions about the central tendencies, variability, and presence of outliers in each dataset. This detailed analysis helps to understand the underlying patterns and differences across various phases and types. PTV ensures comprehensive tumor coverage despite patient movement and variations, enhancing treatment effectiveness. The matching index, on the other hand, serves as a crucial quality assurance tool, ensuring that the treatment is delivered as planned. Together, these concepts play a vital role in improving patient outcomes by maximizing the therapeutic effect on the tumor while minimizing the impact on healthy tissues. Their effective application requires meticulous planning, precise execution, and continuous evaluation, underscoring the importance of advanced imaging technologies and rigorous quality control protocols in modern radiation therapy.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

ETHICAL DECLARATION

This project involves publicly available datasets. This study is not involved with any patients or any healthy volunteers. Institution Review Board approved Protocol Waiver NO: EC/WV/TMC/23/24.

AUTHORS CONTRIBUTION

Concept and data collection by Arun Balakrishnan; Guidance and supervision by P. Ramesh Babu; Manuscript evaluation and modification by Arun Balakrishnan and P. Ramesh Babu.

DATA AVAILABILITY

If apply to your research Data is available on request.

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