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Importance of four-dimensional computed tomography simulation in locally advanced lung cancer radiotherapy: impact on reducing planning target volume

Značaj simulacije četvorodimenzionalnom kompjuterizovanom tomografijom u radioterapiji lokalno uznapredovalog karcinoma pluća: uticaj na smanjenje planiranog ciljnog volumena

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Abstract

Background/Aim. Four-dimensional (4D) computed tomography (CT) simulation is a useful tool for motion assessment in lung cancer radiotherapy. Conventional three-dimensional (3D) free-breathing (FB) simulation is static, with limited motion information on respiratory movements that can produce inaccuracies in the delineation process and radiotherapy planning. The aim of this study was to compare clinically significant differences between the target volumes defined on 3D CT vs. 4D CT simulation and the potential impact on the planning target volume (PTV), bearing in mind that a reduced PTV with precise coverage of the primary tumor is extremely important. In addition, quantification of movements of the primary tumor (gross tumor volume – GTV) was performed during 4D CT simulation on three axes: Z-superoinferior (SI), X-mediolateral (ML), and Y-anteroposterior (AP). **Methods.** This retrospective study evaluated 20 lung cancer patients who underwent CT simulation for radical radiotherapy treatment. FB 3D CT and 4D CT simulations were acquired for each patient in accordance with our institutional protocol. A volumetric comparison of radiation volumes defined on 3D CT vs. 4D CT simulation was done on the following: GTV 3D vs. internal GTV (IGTV) 4D and PTV 3D vs. internal PTV (IPTV) 4D. The comparison of GTV movement in the FB phase GTV (GTV FB), phase 0 (GTV 0), phase 50 (GTV 50), and phase maximum intensity projection (GTV MIP) was made with GTV FB as the basic value. The evaluation was made on all three axes. **Results.** The comparison of volumetric values between GTV 3D vs. IGTV 4D was 63.15 cm^3 vs. 85.51 cm^3 ($p < 0.001$), respectively. IGTV 4D was significantly larger than GTV 3D ($p < 0.001$). The mean value of equivalent spherical diameter (ESD) for PTV 3D vs. IPTV 4D was 8.44 cm vs. 7.82 cm ($p < 0.001$), respectively, and the mean value volume PTV 3D vs. IPTV 4D was 352.70 cm^3 vs. 272.78 cm^3 ($p < 0.001$), respectively. PTV 3D was significantly larger than IPTV 4D ($p < 0.001$). A statistically significant difference ($p < 0.05$) was identified in the deviation related to the Z-axis between the upper and lower lobe. **Conclusion.** 4D CT simulation-based delineation can reduce PTV compared to 3D simulation-based radiation therapy; therefore, it is a prerequisite for high-quality and precise radiation therapy treatment.

Key words:
adenocarcinoma; carcinoma, squamous cell; four-dimensional computed tomography; lung neoplasms; radiotherapy.

Apstrakt

Uvod/Cilj. Simulacija putem četvorodimenzionalne kompjuterizovane tomografije (4D KT) je važan segment savremene radioterapije karcinoma pluća. Konvencionalna trodimenzionalna (3D) simulacija uz slobodno disanje (*free-breathing* – FB) je statična sa limitiranim informacijama o respiratornim pokretima koji mogu produkovati nepreciznosti u procesu delineacije i planiranju radioterapije. Cilj ove studije bio je da se uradi poređenje ciljnih volumena definisanih na 3D KT simulaciji vs. 4D KT simulaciji i uticaja na planirani ciljni volumen (PCV), imajući u vidu da je

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smanjeni PCV uz preciznu pokrivenost primarnog tumora od izuzetne važnosti. Urađena je kvantifikacija pokreta primarnog tumora (*gross tumor volume* – GTV) tokom 4D KT simulacije duž tri ose: Z-superoinferiornu (SI), X-mediolateralnu (ML), Y-anteroposteriornu (AP). **Metode.** U ovoj retrospektivnoj studiji evaluirano je 20 pacijenata sa dijagnozom lokalno uznapredovalog karcinoma pluća i indikacijom za radikalnu radioterapiju. Prema institucionalnom protokolu uradjena je 3D KT i 4D KT simulacija FB za svakog pacijenta. Zatim je urađeno volumetrijsko poređenje volumena definisanih putem 3D KT vs. 4D KT: GTV 3D vs. unutrašnji GTV (UGTV) 4D i PCV 3D vs. unutrašnji PCV (UPCV) 4D. Poređenje pomeranja GTV u fazi FB (GTV FB), fazi 0 (GTV 0), fazi 50 (GTV 50) i fazi projekcije maksimalnog intenziteta, *maximum intensity projection* (GTV MIP) urađeno je tako da je GTV FB uzet kao bazična vrednost. Evaluacija je urađena za sve tri ose. **Rezultati.** Izmerene vrednosti volumena GTV 3D vs. UGTV 4D bile su 63,15 cm^3 vs. 85,51 cm^3 ($p < 0,001$). UGTV 4D je bio značajno veći u odnosu na GTV 3D ($p < 0,001$). Srednja vrednost ekvivalentnog sfernog dijametra (ESD) za PCV 3D vs. UPCV 4D bila je 8,44 cm vs. 7,82 cm ($p < 0,001$), srednja vrednost volumena PCV 3D vs. UPCV 4D bila je 352,70 cm^3 vs. 272,78 cm^3 ($p < 0,001$). PCV 3D je bio značajno veći u poređenju UPCV 4D ($p < 0,001$). Utvrđena je i statistički značajna razlika ($p < 0,05$) u odstupanju GTV u odnosu na Z osovinu između gornjeg i donjeg lobusa. **Zaključak.** Delineacija bazirana na 4D KT simulaciji daje mogućnost redukcije PCV u poređenju sa 3D simulacijom i čini važan preduslov za visoko kvalitetan i precizan radioterapijski tretman.

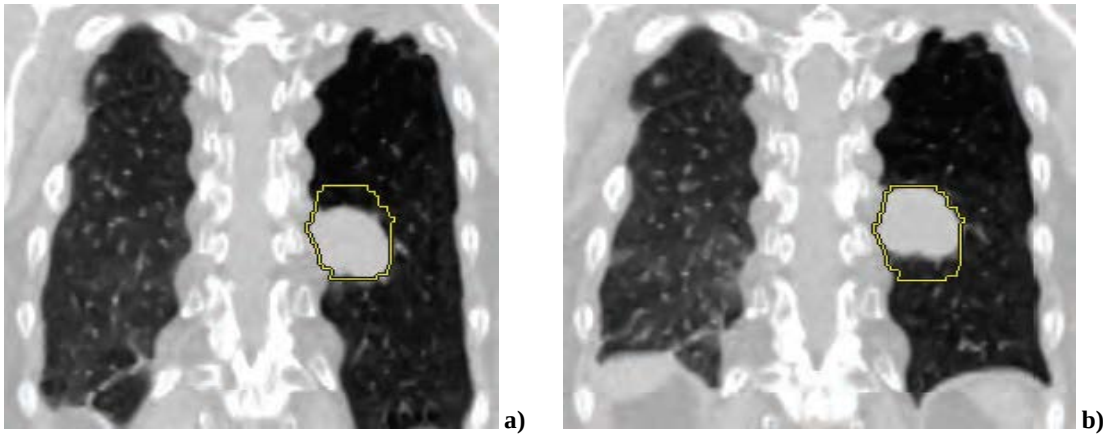
Ključne reči:
adenokarcinom; karcinom, planocelularni; tomografija, kompjuterizovana, četvorodimenzionalna; pluća, neoplazme; radioterapija.

Introduction

Lung cancer is the main cause of cancer death in men and women, presenting almost 20% of all cancer deaths [1]. Non-small cell lung cancer (NSCLC) is the most common histological form found in 85% of newly diagnosed lung cancer cases. In the first presentation, more than 60% of patients are shown in the stage of locally advanced or metastatic disease [2].

Locally advanced stage shows patients with clinical tumor, node, metastasis (TNM) status IIIA, IIIB, IIIC, and the real challenge for radiation therapy is to deliver radical dose to advanced and complex target volumes [3]. Radiotherapy has a crucial role in the radical treatment of locally advanced lung cancer. Its primary purpose is to administer higher doses to the tumor and lower to the surrounding organs at risk in order to maximize tumor control and minimize treatment-related toxicities [4]. In the 1980s, with the introduction of computed tomography (CT) into the planning process, 3D CT became the standard in lung cancer radiotherapy [5]. Assessment and accounting of respiratory motion are vital issues in lung cancer radiotherapy. Historically, respiratory motion management was resolved by adding large planning margins, which imposes a reduction of prescription doses below radical. Technological progress over the last decades with different motion compensation strategies provides more precise and accurate management of respiratory motion during radiotherapy treatment. Respiratory gating can be achieved with external markers (e.g., Varian RPM respiratory gating system) or internal markers as surrogates of tumor motion [6].

Intensity-modulated radiation therapy (IMRT) is a modern and innovative technology increasingly used in contemporary radiation therapy centers [7]. 4D CT simulation is an integral part of IMRT. Modern 4D CT scanners can image the whole thorax and capture all the respiratory cycle phases in less than a minute [8]. Scans obtained during the 4D CT simulation show that more than 50% of lung tumors move more than 5 mm during treatment, while 11% have movements larger than 1 cm [9]. The position of the tumor lesion during inspiration and expiration is shown in Figure 1. The 4D CT simulation enables superior visualization of the target volume and adequate monitoring of respiratory movements during the treatment planning and treatment delivery phase. There are two primary components of the motion: volumetric changes in the target and positional changes of the targets as well as the surrounding organs. The ultimate goal of varied motion management



a) **b)**

Fig. 1 – Tumor volume position during: a) inspiration; b) expiration.

strategies is to detect anatomical motion and adjust radiation therapy accordingly [10].

Due to variations in the position of the target volume during the respiratory cycle, it is impossible to account for the change of the target motion in the course of 3D free-breathing (FB) simulation. In this sense, there is a need to correct this geometric uncertainty in 3D CT. Consequently, these actions pose a larger definitive planning target volume and higher toxicity of surrounding organs at risk [11]. The primary aim of this study was to make a volumetric comparison of the target volumes defined in 3D CT vs. 4D CT simulation and the impact on definitive planning target volume (PTV) in locally advanced lung cancer radiotherapy. Additionally, the movement of gross tumor volume (GTV) in different phases with GTV FB as the basic value was observed in order to determine the significance of the movement assessment and 4D simulation for an adequate target volume coverage.

Methods

Patient selection

The study group included 20 patients with locally advanced lung cancer treated with radical radiotherapy intent at the Radiotherapy Department from September 2018 to January 2020. The patients were identified retrospectively, and 3D and 4D CT scan data were analyzed. The study was approved by the Institutional Review Board (No 03/2020, from October 06, 2020). All patients provided written informed consent prior to the treatment planning.

Data acquisition

3D CT and 4D CT images (2.5 mm slice thickness) were sequentially acquired for each patient. The simulation session was performed in an adequate treatment position (supine position with arms above the head) and with adequate immobilization (All-in-One breast- and lungboard solution – Orfit industries, Wijengem, Belgium) on a GE Lightspeed multislice CT (General Electric Medical System, Waukesha WI). The first CT images were acquired while the patient was FB in a 3D CT data set. 4D CT images were acquired after that using an external respiratory gating system (Real Time Positioning Management System-Varian Medical Systems Inc. Palo Alto, CA, USA). With Advantage 4D system application, sets of images were acquired and classified in ten equally divided breathing phases according to the respiratory cycle (0–100%) labeled as CT_0, CT_{10}, CT_{20}, … and CT_{90}.

Using the appropriate software tools on a 4D CT workstation, the synthesis of CT images was made and created: Max IP – maximum intensity projection, presenting any position where the tumor is present during all respiratory phases; Min IP – minimum intensity projection, presenting one position where the tumor is constantly present in all respiratory phases; Mean IP – mean intensity projection which represents the temporal presence of the tumor in certain respiratory phases.

Then, CT images were transmitted to Varian Eclipse (Varian Medical Systems, Palo Alto, CA, USA) treatment planning system (TPS).

3D CT-based delineation

Target volumes delineation was performed on the 3D CT FB data set according to our institutional protocol, International Commission on Radiation Units and Measurements ICRU 50 and 61 recommendations for 3D CT [12]. GTV 3D was manually contoured and encompassed the primary tumor lesion visualized on FB CT data set images at the window level. Clinical target volume (CTV) 3D was defined with 6–8 mm [squamous cell carcinoma (SCCA), 6 mm; adenocarcinoma (AC), 8 mm] expansion of GTV, including all subclinical lesions and possible areas of infiltration. Planning target volume (PTV) 3D was derived from CTV 3D plus conventional margin 1cm axial, 1.5 cm superior and inferior margin to incorporate setup errors and respiratory motion (Figure 2). The 3D radiotherapy plan is shown in Figure 3.

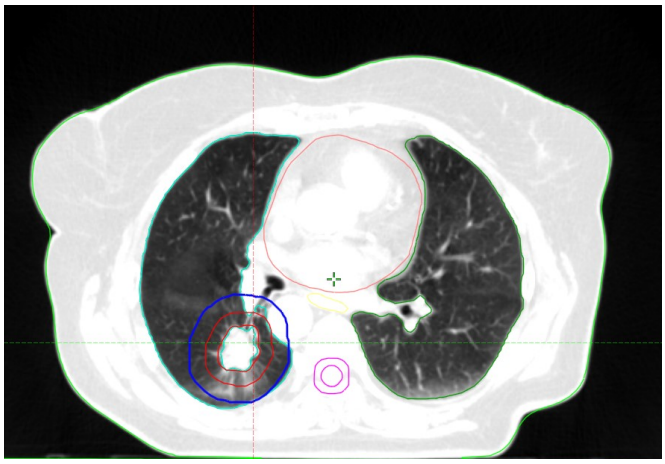


Fig. 2 – 3D conformal-based contouring.
Light red – gross tumor volume (GTV); dark red – clinical target volume (CTV); blue – planning target volume (PTV).

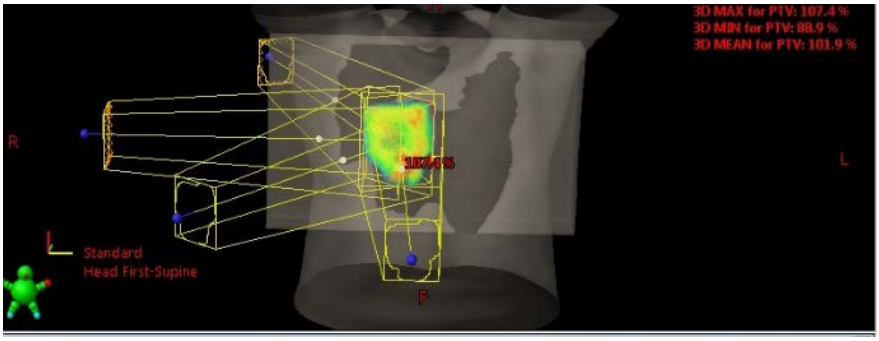


Fig. 3 – 3D conformal plan for radiotherapy treatment.

4D CT simulation-based delineation

4D CT-based radiotherapy volume definition was made following our institutional protocol and ICRU 83 recommendations for IMRT [13].

GTV 4D was manually contoured at the lung window level in different phases in 4D CT images: phase 0 – GTV 0 (which is the end of inspiration), phase GTV 50 (which is the end of expiration), GTV FB (free-breathing phase), GTV MIP (summation of average tumor position in all ten phases of the breathing cycles). For each patient, GTV 0, GTV 50, GTV FB, and GTV MIP were combined in one unique volume defined as internal – IGTV 4D, which represents the precise contour of GTV (Figure 4). Internal CTV (ICTV) 4D was defined with expansion IGTV 4D plus 6–8 mm (SCCA 6 mm, AC 8 mm) based on previous studies [14]. Internal PTV (IPTV) 4D was derived from ICTV 4D plus 0.5 mm isotropic expansion to incorporate setup error only. Delineation of surrounding organs at risk was performed (heart, oesophagus, spinal cord, lungs) according to RTOG recommendations and our institutional protocol [15]. IMRT plan is shown in Figure 5.

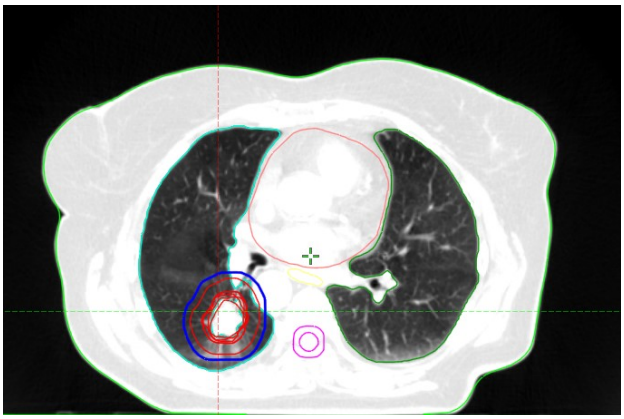


Fig. 4 – 4D intensity modulated radiation therapy (IMRT) contouring. Dark red – internal gross tumor volume (IGTV): GTV 0+GTV 50+GTV free-breathing (FB)+GTV maximum intensity projection (MIP); light red – internal clinical target volume (ICTV); blue – internal planning target volume (IPTV).

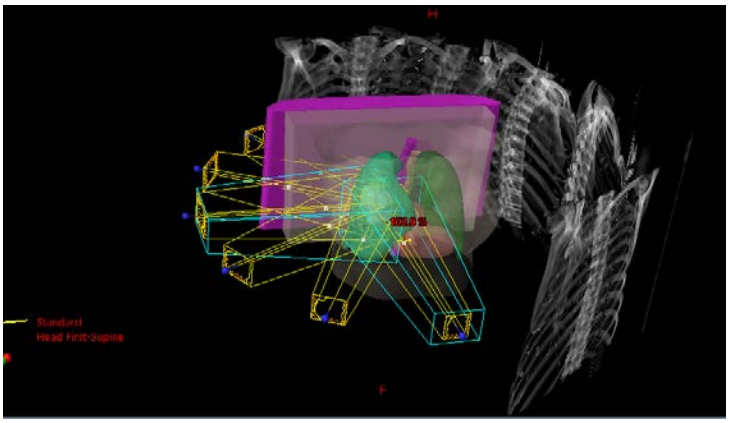


Fig. 5 – 4D-based intensity modulated radiation therapy (IMRT) plan for radiotherapy treatment.

Evaluation of 3D CT vs. 4D CT delineation data sets

Quantitative differences from both imaging data sets – 3D CT-based vs. 4D CT-based simulation were evaluated. Volumetric values GTV 3D, CTV 3D, and PTV 3D vs. volumetric values IGTV 4D, ICTV 4D, and IPTV 4D on two data sets expressed in cm^3 were evaluated. Equivalent spherical diameter (ESD) of GTV 3D, CTV 3D, and PTV 3D vs. ESD of IGTV 4D, ICTV 4D, and IPTV 4D on two data sets expressed in cm were evaluated. An evaluation was conducted by comparing both values.

Due to an objective possibility that a lower percentage of lungs would be irradiated in patients with larger lung volume and a higher percent of lungs would be irradiated in patients with a smaller lung volume when their PTV, CTV, and GTV are equal, the ratios of GTV/total lung, CTV/total lung, PTV/total lung were assessed and analyzed.

Total lung volume (TLV) is the bilateral lung volume (right lung volume plus left lung volume) and the volume of bilateral lungs excluding GTV 3D, CTV 3D, PTV 3D–GTV 3D/total lung ratio, CTV 3D/total lung ratio, and PTV 3D/total lung ratio was expressed in percentages.

TLV excluding IGTV 4D, ICTV 4D, IPTV 4D – IGTV 4D/total lung ratio, ICTV 4D/total lung ratio, and IPTV 4D/total lung ratio were expressed in percentages. Finally, evaluation was made by comparing the extracted volumes from 3D and 4D data sets.

Additionally, in this study, quantification of movements for primary tumor (GTV) during 4D IMRT in three axes was performed. A comparison of GTV movements was made with GTV FB as the basic value.

Statistical analysis

Measured data are presented in graphs and tables with original measurements or standard descriptive statistical measures – the sample means and sample standard deviations (mean ± SD). The data were analyzed by fitting general linear mixed models (GLMM), while in the case of significant differences in variation between the studied groups, an appropriate post-hoc analysis was conducted by testing variances between the means applying the standard pairwise test procedure. Pearson correlation coefficient (r) was also calculated. The results of the analysis were discussed in view of practical and statistical significance. Results of the analysis in terms of the observed differences between the studied groups were deemed statistically significant in case $p < 0.05$. Statistical analysis and graphical representation of data were prepared with the support of SPSS 22 software (IBM, 2013).

Results

The patients' characteristics are described in Table 1. A total of 20 patients were included and analyzed in this study. The average age of the study group was 70.8 years, with a range of 50–78 years. Most of the patients (60%) had the TNM stage IIIA. Eleven patients had pathological verified AC, and nine had SCCA. Fourteen patients were male, and six were female. Localization of the tumor was peripheral in 11 patients, and central localization was verified in 9 patients.

Statistical analysis of mean volumes generated on 3D and 4D data sets is shown in Table 2. The mean value of

Table 1

Patient characteristics

Parameters	Values
Total number of patients, n (%)	20 (100)
Age (years), mean (range)	70.8 (50–78)
Tumor, n (%)	
AC	11 (55)
SCCA	9 (45)
Gender, n (%)	
male	14 (70)
female	6 (30)
Tumor localization, n (%)	
central	9 (45)
peripheral	11 (55)
Lobe, n (%)	
RUL	4 (20)
RML	4 (20)
RLL	4 (20)
LUL	3 (15)
LLL	3 (15)
Lingula	2 (10)
TNM, n (%)	
III A	12 (60)
III B	5 (25)
III C	3 (15)

AC – adenocarcinoma; SCCA – squamous cell carcinoma; RUL – right upper lobe; RML – right middle lobe; RLL – right lower lobe; LUL – left upper lobe; LLL – left lower lobe; TNM – tumor, node, metastasis.

Table 2

A volumetric comparison of radiation volumes 3D simulation-based data set vs. 4D computed tomography-based simulation data set

Radiation volume	ESD (cm)		Volume (cm^3)		Lung/volume ratio (%)	
	Mean	SE	Mean	SE	Mean	SE
GTV 3D	4.40	0.34	63.15	14.43	1.63	0.42
IGTV 4D	5.12	0.31	85.51	16.96	2.20	0.50
CTV 3D	6.16	0.38	152.27	27.63	3.84	0.79
ICTV 4D	6.79	0.33	183.30	29.59	4.62	0.85
PTV 3D	8.44	0.38	352.70	46.65	8.78	1.34
IPTV 4D	7.82	0.32	272.78	36.39	6.81	1.05
F	364.76		43.33		32.65	
p	< 0.001		< 0.001		< 0.001	

GTV – gross tumor volume; IGTV – internal GTV; CTV – clinical target volume; ICTV – internal CTV; PTV – planning target volume; IPTV – internal PTV; ESD – equivalent spherical diameter; SE – standard error.

ESD GTV 3D vs. IGTV 4D was 4.40 cm vs. 5.12 cm ($p < 0.001$), respectively. The mean volumetric value of GTV 3D vs. IGTV 4D was 63.15 vs. 85.51cm^3 ($p < 0.001$), respectively. IGTV 4D was significantly larger than GTV 3D ($p < 0.001$).

The mean value of ESD CTV 3D vs. ICTV 4D was 6.16 cm vs. 6.79 cm ($p < 0.001$), respectively. The mean volumetric value of CTV 3D vs. ICTV 4D was 152.27 cm^3 vs. 183.30 cm^3 ($p < 0.001$), respectively. ICTV 4D was significantly larger than CTV 3D ($p < 0.001$) (Figures 6 and 7).

The mean value of ESD PTV 3D vs. IPTV 4D ESD was 8.44 cm vs. 7.82 cm ($p < 0.001$), respectively. The mean volumetric value PTV 3D vs. IPTV 4D ESD was 352.70 cm^3 vs. 272.78 cm^3 ($p < 0.001$), respectively. PTV 3D was significantly larger than IPTV 4D ($p < 0.001$) (Figures 6 and 7).

The mean value GTV 3D/total lung ratio vs. IGTV 4D/total lung ratio was 1.63 vs. 2.20 ($p < 0.001$), respectively. The mean value CTV 3D/total lung ratio vs. ICTV 4D/total lung ratio was 3.84 vs. 6.62 ($p < 0.001$), respectively.

The mean value PTV 3D/total lung ratio vs. IPTV 4D total lung ratio was 8.78 vs. 6.81 ($p < 0.001$), respectively. The results of these comparisons are shown in Table 2.

IGTV 4D/total lung ratio and ICTV 4D/total lung ratio were significantly larger than GTV 3D/total lung ratio and CTV 3D/ total lung ratio ($p < 0.001$), respectively.

The definitive PTV 3D/total lung ratio was significantly larger than IPTV 4D/total lung ratio ($p < 0.001$), respectively (Figure 8). Correlations between the measured variables are shown in Table 3.

Figure 9 shows a graphical presentation of the tumor position for each patient in the X, Y, and Z-axis. There was almost no dislocation along the X and Y-axes when assessed in phases GTV 0, GTV 50, GTV FB, or GTV MIP. Analysis of dislocation along the Z-axis indicated that the difference between the studied phases was highly significant ($p < 0.001$).

When different breathing phases were compared, a statistically significant difference in the movement along the X-axis ($p = 0.931$) was not identified. The result of the movement along the Y-axis was similar, with no statistically significant difference ($p = 0.524$).

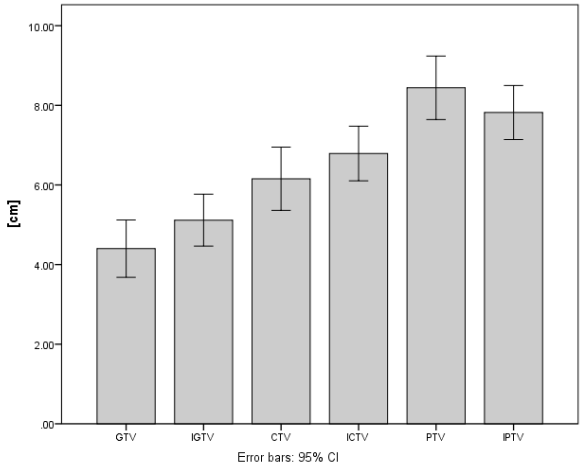


Fig. 6 – Comparison of equivalent spherical diameter (ESD) volumetric values of radiation volumes GTV 3D, CTV 3D, and PTV 3D vs. IGTV 4D, ICTV 4D, and IPTV 4D expressed in cm.
GTV – gross tumor volume; IGTV – internal GTV; CTV – clinical target volume; ICTV– internal CTV; PTV – planning target volume; IPTV – internal PTV; CI – confidence interval.

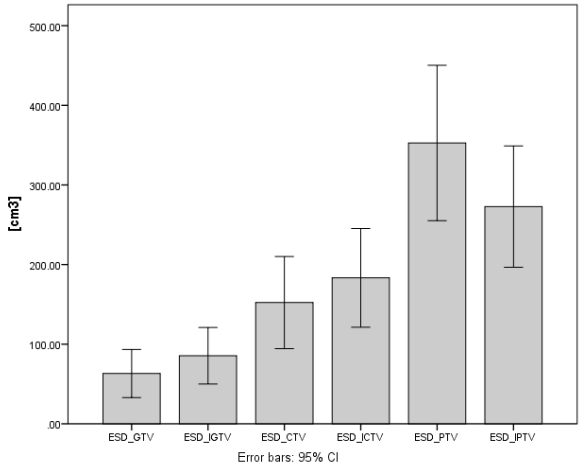


Fig. 7 – Comparison of values of radiation volumes for GTV 3D, CTV 3D, and PTV 3D vs. IGTV 4D, ICTV 4D, and IPTV 4D expressed in cm^3.
ESD – equivalent spherical diameter; GTV – gross tumor volume; IGTV – internal GTV; CTV – clinical target volume; ICTV – internal CTV; PTV – planning target volume; IPTV – internal PTV; CI – confidence interval.

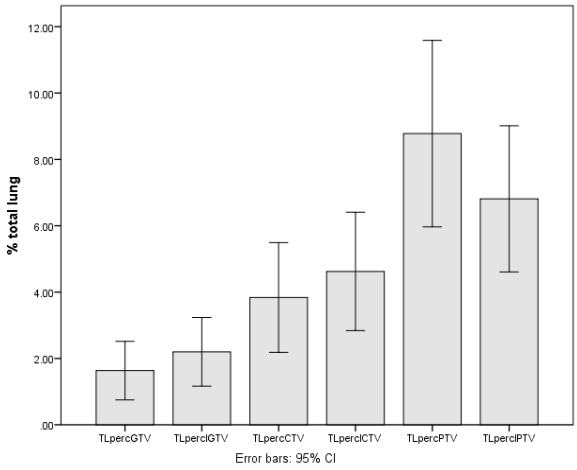


Fig. 8 – Comparison of GTV 3D, CTV 3D, and PTV 3D/total lung ratio vs. IGTV 4D, ICTV 4D, and IPTV 4D/total lung ratio expressed in percentages (%); CI – confidence interval. TL – total lung; GTV – gross tumor volume; IGTV – internal GTV; CTV – clinical target volume; ICTV – internal CTV; PTV – planning target volume; IPTV – internal PTV; CI – confidence interval.

Table 3

Correlation coefficients (r) between measured variables

Variables	GTV	IGTV	CTV	ICTV	PTV	IPTV
GTV	1	0.991	0.968	0.969	0.897	0.92
IGTV	0.991	1	0.967	0.974	0.91	0.93
CTV	0.968	0.967	1	0.988	0.973	0.977
ICTV	0.969	0.974	0.988	1	0.96	0.979
PTV	0.897	0.91	0.973	0.96	1	0.989
IPTV	0.92	0.93	0.977	0.979	0.989	1

GTV – gross tumor volume; IGTV – internal GTV; CTV – clinical target volume; ICTV – internal CTV; PTV – planning target volume; IPTV – internal PTV.

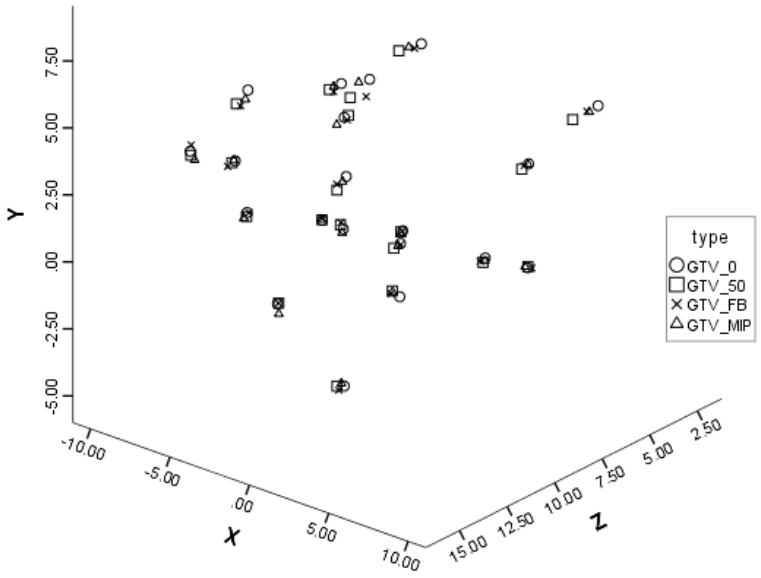


Fig. 9 – Graphical presentation of tumor position (GTV) in different breathing phases (GTV 0, GTV 50, GTV FB, GTV MIP) along X, Y, Z-axis during the breathing cycle; Z – superoinferior (SI), X – mediolateral (ML), Y –anteroposterior (AP). GTV– gross tumor volume; FB – free-breathing; MIP – maximum intensity projection.

The highest values were obtained in the GTV MIP phase, compared to all other phases. Phases GTV FB and GTV 50 did not differ significantly and were placed between GTV 0 and GTV MIP values.

Discussion

Precise and safe delivery of radiation dose to a tumor that moves with respiration is a real clinical and technical challenge. Technically, safe delivery of thoracic radiotherapy involves multiple factors: precise CT imaging, positioning, precise target volume definition, and adequate control of the breathing motion [16]. In the context of locally advanced lung cancer radiotherapy and complex radiation volumes with significant respiratory motion, the addition of various geometric margins leads to the irradiation of a larger volume of healthy tissue, consequently increasing the risk of complications while reducing the possibility of dose escalation [17]. Incorporating tumor motion in the radiotherapy process in order to increase effective tumor targeting and allow a reduction in the planning target volume is a very important issue [18]. In principle, if imaging and treatment are synchronized with the patient's respiratory cycle, there is the potential for CTV-PTV margin reduction [19].

Different retrospective studies have previously evaluated the significance of 4D CT simulation in radical lung cancer radiotherapy treatment. Ahmed et al. [19] made an evaluation to find out if the motion assessment with 4D CT simulation improved the target coverage in lung cancer radiotherapy and showed superior coverage of the target volume compared to 3D simulation. IGTV 4D was significantly larger than GTV 3D for both primary and nodal diseases, either combined or separately. The results of our study are comparable with the above-mentioned results – volumetric value IGTV 4D expressed in cm^3 and ESD IGTV 4D expressed in cm were significantly larger than GTV 3D. This result is expected, given that IGTV 4D is combined after delineating GTV in ten breathing phases, while GTV 3D is delineated only in the FB phase. Correlating lung tumor location and motion with respiration using a 4D CT scan was evaluated by Siow and Lim [20], who emphasized the importance of motion mitigation strategies.

A further evaluation made for this study showed a statistically significant difference between PTV 3D vs. IPTV 4D. The volumetric values and equivalent spherical diameter of PTV were significantly reduced in 4D simulation-based delineation in this study. PTV 3D in both cases was significantly larger than IPTV 4D. That is a very significant result. It is essential to minimize the exposed planning target volume in patients with locally advanced lung cancer and large tumor volume because normal lungs and organs at risk are exposed at large radiation volumes and, consequently, higher doses. Various authors suggest that incorporating tumor motion into the simulation, planning, and delivery is necessary for effective tumor targeting, which provides the possibility of reducing PTV and decreasing the dose to organs at risk [21, 22]. Secondary analysis of the RTOG 0617 study demonstrated that IMRT was associated with lower rates of severe pneumonitis and cardiac doses, thereby justifying the use of IMRT for locally advanced non-small cell lung cancer, which improves the target coverage while minimizing radiation to surrounding tissues [23]. Ueyama et al. [24] suggest that both large PTV volume and large PTV/total lung ratio were significantly associated with radiation pneumonitis.

In this study, 3D-based PTV/total lung ratio vs. 4D-based IPTV/total lung ratio expressed in percentages indicated that 3D-based PTV had a significantly larger volume. That is a burning issue; it is extremely important to decrease radiation volume in order to avoid acute and late side effects to surrounding organs at risk. Clinical studies have shown that minimizing the lung volume irradiated even to extremely low doses can result in fewer pulmonary complications [25]. Matsuo et al. [26] reported that large PTV was a significant risk factor for symptomatic radiation pneumonitis. The main disadvantage of the current study is the small number of patients. However, based on these results, this study indicates the benefits of using 4D simulation over 3D simulation-based delineation and the possibility of decreasing definitive PTV.

Given the respiration in various locations of the lungs, tumor motion has already been widely described. A study conducted by Seppenwoolde et al. [27] used gold fiducial markers inserted into tumors and tracked their motion using a real-time tracking system. They concluded that the largest motion was seen in the cranial-caudal direction in the lower lobe tumors near the diaphragm. Another study evaluated lung tumor motion on a large sample. After analyzing more than 500 hours of data, the highest rates of motion amplitudes, intrafraction/interfraction variation, and tumor baseline changes were in the SI direction (6.0 ± 2.2 mm, 2.2 ± 1.8 mm, 1.1 ± 0.9 mm, and -0.1 ± 2.6 mm) [28]. Motion amplitudes >15 mm were observed only in the lower geometric quarter of the lungs.

The results of this study are compatible with the results acquired in previous studies of lung tumor motion. There was almost no dislocation of the tumor along the X and Y-axes when assessed in the phases GTV 0, GTV 50, GTV FB, or GTV MIP. Unlike the movement along the X and Y-axes, dislocation along the Z-axis (superoinferior) was observed in almost half of the studied cases. When different breathing phases were compared, no statistically significant difference was identified in the movement along the X-axis. Similar results were acquired by the analysis of movement along the Y-axis, i.e., there was no statistically significant difference. The analysis of dislocation along the Z-axis indicated that the difference between the studied phases was highly significant.

An obvious advantage of 4D CT is the possibility of synchronizing the radiation beam with the moving target, and hence it is an important segment of modern and precise radiotherapy. A possible adverse aspect of the 4D CT simulation-based radiotherapy approach is the additional infrastructure required for obtaining 4D CT, personal training, and education of patients, as well as the increased workload for radiation oncologists in the delineation process, compared to 3D simulation-based radiotherapy.

Conclusion

Radiotherapy treatment of lung cancer has entered the era of precision medicine and radiotherapy. Determination of the target area is the key point in radiotherapy.

With 4D CT, personalized approach with individualized patient's margins that encompasses patients breathing motion becomes possible. This study suggests that 4D simulation is an important issue in lung cancer radiotherapy that poses high precision treatment with possibly reduced planning target volume and consequently reduced side effects of radiotherapy.

REFERENCES

1. *Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A,* et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021; 71(3): 209–49.
2. *Ettinger DS, Wood DE, Aisner LD, Akerley W, Bauman RJ, Bharat A*, et al. NCCN guidelines Insights: Non-small cell lung cancer version 2.2021. J Natl Compr Canc Netw 2021; 19(3): 254–66.
3. International Association for the Study of Lung. Staging Manual in Thoracic Oncology. 2nd ed. North Fort Myers, FL: IASLC; 2016.
4. *Park K, Vansteenkiste J, Lee HK,Peters S, Toshino J, Douillard JY*. Pan - Asian adapted ESMO Clinical Practical Guidelines for the management of patients with locally advanced unresectable non-small lung cancer: a KSMO-ESMO initiative endorsed by CSCO, ISMPO, JSMO, MOS, SSO and TOSS. Ann Oncol 2020; 31(2): 191–201.
5. *Fromm S, Rottenfusser, Berger D, Pirker R, Pötter R, Pokrajac B*. 3D conformal radiotherapy for inoperable non-small cell lung cancer- a single center experience. Radiol Oncol 2007; 41(3): 133–43.
6. *Dhont J, Harden SV, Chee LYS, Aitken K, Hanna GG, Bertholet J*. Image-guided Radiotherapy to Manage Respiratory Motion: Lung and Liver. Clin Oncol (R Coll Radiol) 2020; 32(12): 792–804.
7. *Boyle J, Ackerson B, Gu L, Kelsey CR*. Dosimetric advantages of intensity modulated radiation therapy in locally advanced lung cancer. Adv Radiat Oncol 2017; 2(1): 6–11.
8. *Steiner E, Shieh CC, Caillet V, Booth J, O'Brien R, Briggs A*, et al. Both four-dimensional computed tomography and four-dimensional cone beam computed tomography under-predict lung target motion during radiotherapy. Radiother Oncol 2019; 135: 65–73.
9. *Ono T, Nakamura M, Hirose Y, Kitsuda K, Ono Y, Ishigaki T*, et al. Estimation of lung tumor position from multiple anatomical features on 4D-CT using multiple regression analysis. J Appl Clin Med Phys 2017; 18(5): 36–42.
10. *Ren XC, Liu YE, Li J, Lin Q*. Progress in image-guided radiotherapy for the treatment of non-small cell lung cancer. World J Radiol 2019; 11(3): 46–54.
11. *Cusumano D, Dhont J, Boldrini L, Chiloiro G, Teodoli S, Massacessi M*, et al. Predicting tumor motion during the whole radiotherapy treatment: a systematic approach for thoracic and abdominal lesions based on real time MR. Radiother Oncol 2018; 129(3): 456–62.
12. *Chavaudra J, Bridier A*. Definition of volumes in external radiotherapy: ICRU reports 50 and 62. Cancer Radiother 2001; 5(5): 472–8. (French)
13. International Commission on Radiation Units and Measurements. Prescribing, recording and reporting photon beam intensity modulated radiation therapy. ICRU report 83. Bethesda, MD: ICRU; 2010.
14. *Giraud P, Antoine M, Larrouy A, Milleron B, Callard P, De Rycke Y,* et al. Evaluation of microscopic tumor extension in non-small-cell lung cancer for three-dimensional conformal radiotherapy planning. Int J Radiat Oncol Biol Phys 2000; 48(4): 1015–24.
15. *Kong FM, Ritter T, Quint DJ, Senan S, Gaspar LE, Komaki RU,* et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. Int J Radiat Oncol Biol Phys 2011; 81(5): 1442–57.
16. *Mercieca S, Belderbos JSA, van Herk M*. Challenges in the target volume definition of lung cancer radiotherapy. Transl Lung Cancer Res 2021; 10(4): 1983–98.
17. *Nestle U, Le Pechoux C, De Ruysscher D*. Evolving target volume concepts in locally advanced non-small cell lung cancer. Transl Lung Cancer Res 2021; 10(4): 1999–2010.
18. *Wilke L, Andratschke N, Blanck O, Brunner TB, Combs SE, Grosu AL*, et al. ICRU report on prescribing, recording and reporting of stereotactic treatments with small beam photons:Statements from DEGRO/DGMP working group stereotactic radiotherapy and radiosurgery. Strahlenter Onkol 2019; 195(3): 193–8.
19. *Ahmed N, Venkataraman S, Johnson K, Sutherland K, Loewen SK*. Does Motion Assessment With 4-Dimensional Computed Tomographic Imaging for Non-Small Cell Lung Cancer Radiotherapy Improve Target Volume Coverage? Clin Med Insights Oncol 2017; 11: 1179554917698461.
20. *Siow T, Lim S*. Correlating lung tumor location and motion with respiration using 4DCT scan. J Radiother Pract 2021; 20(1): 17–21.
21. *Molitoris JK, Diwanji T, Snider JW 3rd, Mossahebi S, Samanta S, Badiyan SN,* et al. Advances in the use of motion management and image guidance in radiation therapy treatment for lung cancer. J Thorac Dis 2018; 10(Suppl 21): S2437–50.
22. *Diwanji TP, Mohindra P, Vyfhuis M, Snider JW 3rd, Kalavagunta C, Mossahebi S,* et al. Advances in radiotherapy techniques and delivery for non-small cell lung cancer: benefits of intensity-modulated radiation therapy, proton therapy, and stereotactic body radiation therapy. Transl Lung Cancer Res 2017; 6(2): 131–47.
23. *Chun SG, Hu C, Choy H, Komaki RU, Timmerman RD, Schild SE,* et al. Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non-Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial. J Clin Oncol 2017; 35(1): 56–62.
24. *Ueyama T, Arimura T, Takumi K Nakamura F, Higashi R, Ito S*, et al.. Risk factors for radiation pneumonitis after stereotactic radiation therapy for lung tumors: clinical usefulness of the planning target volume to total lung volume ratio. Br J Radiol 2018; 91(1086): 20170453.
25. *Meng Y, Yang H, Wang W, Tang X, Jiang C, Shen Y,* et al. Excluding PTV from lung volume may better predict radiation pneumonitis for intensity modulated radiation therapy in lung cancer patients. Radiat Oncol 2019: 14(7): doi.org/10.1186/s13014-018-120-x.
26. *Matsuo Y, Shibuya K, Nakamura M, Narabayashi M, Sakanaka K, Ueki N*, et al.. Dose volume metrics associated with radiation pneumonitis after stereotactic body radiation therapy for lung cancer. Int J Radiat Oncol Biol Phys 2012; 83(4): e545–9.
27. *Seppenwoolde Y, Shirato H, Kitamora K, Shimizu S, van Herk M, Lebesque JV,* et al. Precise and real-time measurement of 3-D tumor motion in lung due to breathing and heartbeat, measured during radiotherapy. Int J Radiat Oncol Biol Phys 2002; 53(4): 822–34
28. *Knybel L, Cvek J, Molenda L, Stieberova N, Feltl D*. Analysis of Lung Tumor Motion in a Large Sample: Patterns and Factors Influencing Precise Delineation of Internal Target Volume. Int J Radiat Oncol Biol Phys 2016; 96(4): 751–8.

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