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Lung Organ-at-Risk volumes – A survey of practice and the need for a consistent definition in the 4DCT era

Running Title

Definition of Lung Organ-at-Risk volumes in the 4DCT era

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Lung Organ-at-Risk volumes – A survey of practice and the need for a consistent definition in the 4DCT era

Abstract

Introduction

In the 4DCT era, the definition of lung organ-at-risk (OAR) volumes for dose volume histogram (DVH) calculation is unclear, introducing potential for variability in practice. We aimed to identify definitions used clinically and evaluate the magnitude of DVH differences between these.

Methods

We surveyed Australian & New Zealand departments about lung radiotherapy protocols including lung OAR volume definition. We used these definitions to calculate lung DVHs on 10 patients prescribed lung IMRT (60-66Gy/30-33 fractions). We calculated mean lung dose (MLD), V20 and V30 for "Lungs – PTV", "Lungs – CTV", "Lungs – iGTV" (internal GTV in all respiratory phases) and "Lungs – GTV_EX" (expiratory phase).

Results

The response rate was 39% (34/88). 14% and 29% of departments did not have a departmental protocol for OAR and tumour volume delineation respectively. All permutations for lung OAR volumes were used with no clear preference. For conventional radiotherapy (n=27), this included Lungs alone (n=1), Lungs – PTV (n=6), Lungs – CTV (n=2), Lungs – iGTV (n=6), Lungs – GTV in single phase (n=5) and individual clinician preference (n=7). The different lung OAR volumes resulted in MLD difference ranging from 0.9Gy to 4.15Gy, V20 from 1.5% to 6.6% and V30 from 1.34% to 7.11%.

The largest differences between subtraction of GTV_EX and iGTV were 0.32Gy, 0.43% and 0.46% for MLD, V20 and V30 respectively.

Conclusion

A significant number of departments lacked lung cancer radiotherapy contouring protocols. Lung OAR volume definition was variable between and within departments. Potentially clinically significant differences in lung DVH parameters were seen according to the volume used.

Keywords

Dose-response relationship, Radiation

Lung neoplasms

Practice patterns, Physicians

Radiotherapy

Stereotactic body radiotherapy

Manuscript

Introduction

Radiation pneumonitis is usually the dose-limiting toxicity for prescription of radiotherapy doses in the treatment of lung cancer. The risk of this is directly related to the volume of surrounding lung receiving radiotherapy dose[1,2] although this can be influenced by other factors such as chemotherapy[3]. Accurate and consistent volume delineation is therefore crucial to correct interpretation of dose volume histograms (DVHs).[4] However lung organ-at risk volume (OAR) definitions have not been updated in the era of 4 dimensional computed tomography (4DCT). This leaves room for inconsistent interpretation particularly when institutional protocols are derived from published literature without an appreciation of the lung volume calculations underlying a particular DVH parameter.

The studies on which our current lung DVH constraints are based were all conducted in the 3 dimensional computed tomography (3DCT) era and had varying definitions of “lung” for lung DVH calculation. These definitions included “total lung – Planning Target Volume (PTV)”[1,5], “total lung – Clinical Target Volume (CTV)”[6] and “total lung – Gross Target Volume (GTV)”[2].

Further complexity has been added with the advent of stereotactic ablative body radiotherapy (SABR) for lung cancer. Target volume delineation for SABR does not include any margin for CTV and so the only relevant volumes are GTV, ITV and PTV. This results in different definitions of ITV dependent on radiotherapy technique. The Internal Commission on Radiation Units (ICRU) 62 report defines ITV as a margin around the CTV to encompass expected variations in CTV size, shape and physiologic motion.[7] ICRU does not explicitly address the implementation of GTV and OAR definitions in the context of 4DCT based planning for conventional or SABR radiotherapy.

Radiation Therapy Oncology Group (RTOG) 0236, one of the first prospective studies in lung SABR did not mandate 4DCT and lung OAR volume was defined as "Total lung - GTV – trachea and ipsilateral bronchus".[8] The RTOG 0813 trial allowed 4DCT and also different methods of defining the GTV based on 4DCT, however the definition of lung OAR volumes was identical to RTOG 0236.[9] In the recently completed CHISEL trial where 4DCT was mandated, "Total lungs – ITV" was used for lung DVH calculation.[10]

The segmented GTV based on a single phase of the respiratory cycle may have a different volume to the envelope of GTVs throughout the respiratory cycle. Similarly the segmented total lung volume may vary between different datasets.[4] The impact of these variations on the ability to model radiation induced lung toxicity was recently recognised in the lung SABR setting.[11]

The aim of the present work was to identify definitions of lung OAR volumes in lung cancer radiotherapy protocols in Australia and New Zealand and to determine the impact of different lung OAR volume definitions on DVH parameters in a representative patient set.

Methods and Materials

First, we undertook a survey of all Australian and New Zealand departments in 2018 to assess lung cancer protocols and practice and assess how OAR risk volumes were being defined in clinical practice. The survey questions are shown in Appendix 1. The link to the survey was sent out to all radiation oncology department heads in Australia and New Zealand and also to all members of the Faculty of Radiation Oncology Lung Interest Cooperative (FROLIC), with the request to fill this out at a departmental level. The surveys were emailed out in June 2018 and closed in August 2018.

Second, to assess the impact of different volume subtractions on dose volume metrics, we calculated lung DVHs on a cohort of ten consecutive patients who underwent 4DCT simulation and had completed intensity modulated radiotherapy for Stage II-III Non-Small Cell Lung Cancer to a dose of 60-66 Gy/30-33 fractions. Our protocol involved primary and nodal GTV delineation on the expiratory phase of 4DCT (GTV_EX). The expiratory phase was used for delineation as this is the

longer phase of the respiratory cycle where the GTV is positioned for a greater length of time. GTV_EX was then propagated to all phases to create what we have termed internal GTV (iGTV) using MIM v6.7 (MIM Software Inc., Cleveland, OH, USA) software. iGTV is a composite of GTVs in all phases of a 4D CT. Propagation was checked on the cine mode ensuring tumour motion was within the created contour. A margin of 5-8mm was added to the iGTV to create a CTV as per departmental protocol, and a further 5mm from CTV to PTV. The "total lung" volumes were created on the average dataset of the 4DCT scan. These were generated using an automatic threshold based tool and edited using mediastinal window levels. Plans were generated using Pinnacle3® treatment planning system (Philips Radiation Oncology, Madison, WI) using CT slice spacing of 0.2 cm, dose calculation grid size of 0.25 cm^3 and Pinnacle's Adaptive Convolve convolution dose calculation algorithm. We calculated mean lung dose (MLD), V20 and V30 for "Total lung – PTV", "Total lung – CTV", "Total lung – iGTV" and "Total lung – GTV_EX". These parameters were also calculated with "total lung" delineated on the inspiratory and expiratory phases.

Results

Survey results

We received responses from 34 out of 88 radiation oncology departments surveyed (response rate 39%), although not all departments answered every question. The majority of departments had a radiotherapy planning protocol and DVH assessment protocol for both conventional and stereotactic lung radiotherapy. (Figure 1) Less than half the respondents had tumour or OAR delineation protocols for both techniques with 29% not having a departmental protocol for tumour delineation.

There were 11 free text responses for the definitions of GTV, ITV, CTV and PTV used for conventional radiotherapy. GTV was defined as radiologically apparent tumour (primary and nodes) on CT and/or PET scan by seven departments. Six of these departments defined ITV as tumour on all phases of the 4DCT or maximum intensity projection (MIP) then defined CTV as a 5-10mm expansion of their ITV. One department did not use ITV and defined CTV as a 5-10mm expansion of their GTV.

Four departments incorporated respiratory motion in their definition of GTV with the tumour being delineated on MIP or propagated on all phases of the 4DCT with these volumes called iGTV or GTV_RESP by two departments. Three of these departments then defined ITV as a 5-8mm expansion on their GTV and did not use a CTV in their protocol. One department had the same definition for GTV and ITV and defined CTV as ITV with a minimum 5mm margin varying according to the radiation oncologist.

All departments defined PTV as a 5-10mm expansion on either their CTV or ITV, whichever volume was larger, with one department stating larger margins of 10-15mm if respiratory motion had not been accounted for in delineation of earlier volumes.

There were 17 free text responses to the definitions of GTV, ITV, CTV and PTV used for lung SABR. Three defined GTV as radiologically apparent tumour with no mention of the type of simulation scan, three defined this on a free-breathing CT scan, one on the average intensity projection (AIP) of 4D CT scan, six on MIP or all phases of the 4DCT, and two on end-expiration. All these departments defined their ITV as GTV on all phases of a 4DCT and / or MIP with several commenting on the need to check that the ITV contour covered the target in all phases. Two departments did not specifically define a GTV for stereotactic radiotherapy but both these defined their ITV as being based on a MIP or gated CT scan with PET fusion. CTV was not separately defined in for this technique or said to be equivalent to ITV. PTV was defined as a 5-10mm expansion on ITV.

Survey responses on the imaging datasets used for delineation of GTV and lung OAR volumes are shown in Table 1. For curative conventional radiotherapy, the majority of respondents delineated on all phases of 4DCT or MIP. Only 15% used 3DCT alone. For lung SABR, 40% used 4DCT and 16% used MIP. Six departments used an alternative dataset or combination of imaging datasets for GTV delineation both for conventional and stereotactic lung radiotherapy. This included the use of PET CT for simulation or combination of MIP images with one of the other alternatives listed. The majority of OAR contours were delineated on 3DCT (48%) or AIP (37%) scans. The three departments which denoted “other” differentiated between OAR delineation for conventional radiotherapy being on 3DCT and for lung SABR being either on exhale or AIP scans.

All possible permutations for lung OAR volumes were in use for DVH calculation with no clear preference. (Table 2) Some departments subtracted the GTV in all phases of the respiratory cycle, what we have termed “iGTV” whilst others subtracted GTV in one phase of the respiratory cycle. Delineation of the actual lung volumes (n=27 responses) also differed with five departments relying on automated delineation based on their planning systems, six departments using a semi-automated approach with editing on mediastinal windows, 13 using semi-automated approach with editing on lung windows and three stating some other method.

The metrics used to assess lung toxicities were mean lung dose (88%), V20 (96%), V5 (73%) and V30 (19%). The majority of departments accepted a mean lung dose ≤18-20Gy, V20<30-35%, V5<60-65%, and V30<20-25%. The highest accepted values were mean lung dose of 20Gy, V20 of 35%, V5 of 75% and V30 of 25%. When asked what happens if one of more lung DVHs exceeds the tolerance value, 42% stated that the radiation oncologist may still accept the plan with the patient being informed of

the increased risk of lung toxicity and that this would be documented in the notes. Thirty-eight percent stated that further action varied according to the radiation oncologist.

Dose Volume Histograms results

We calculated lung DVHs on a cohort of ten consecutive patients who underwent 4DCT simulation. The different tumour volume subtractions resulted in a difference in MLD ranging from 0.9Gy to 4.15 Gy (Figure 2), V20 from 1.5% to 6.6% (Figure 3) and V30 from 1.35% to 7.11%. Four patients had a difference in MLD greater than 2Gy, seven patients a difference in V20 greater than 2% and eight patients in V30 greater than 2%. Subtraction of the PTV resulted in the lowest DVHs. Larger differences in the DVHs were seen for higher values of MLD and V20. The largest difference between subtraction of GTV_EX and iGTV was 0.32Gy, 0.43% and 0.46% for MLD, V20 and V30 respectively.

Subtraction of the iGTV from different total lung volumes, delineated on the average, inspiratory and expiratory phases resulted in a difference in MLD ranging from 0.44Gy to 2.88Gy and V20 from 0.37% to 5.61%. One patient had a difference in MLD greater than 2Gy and four patients a difference in V20 greater than 2%. There was no consistent lung volume associated with lower DVHs.

Discussion

There is considerable heterogeneity within Australia and New Zealand with respect to departmental protocols for the radiotherapy treatment of lung cancer. Volume delineation is the most crucial step in radiotherapy planning and for lung cancer requires interpretation of multimodality imaging and incorporation of respiratory motion. It is of concern that 29% of departments did not have a tumour volume delineation protocol. It may be that some of these departments use published recommendations such as European Society of Therapeutic Radiation Oncology (ESTRO)[12] or FROLIC[13]. However these recommendations do have to be tailored to local radiotherapy imaging and planning systems and so specific departmental guidelines are preferable.

Fourteen percent of departments did not have a delineation protocol for OARs. These are standard volumes with available atlases such as RTOG[14] for use. However for accurate interpretation of DVHs, it is important to ensure that OARs are being delineated consistently across a department.

All departments had a planning protocol for lung cancer radiotherapy although some departments only had these for a specific technique. It may be that departments who did not have a protocol for stereotactic radiotherapy were not actually delivering this treatment. The Royal Australian and New Zealand College of Radiologists (RANZCR) has published Radiation Oncology Practice Standards covering protocols.[15,16] Criterion 9.1 states that treatment planning protocols should be documented, accessible to staff and endorse evidence-based best practice. Treatment planning

protocols include patient positioning, immobilisation and monitoring, simulation and imaging, contouring and target definition, suggested beam positioning, plan development and evaluation i.e. including all four protocols we asked about in our survey. We have identified a gap which needs to be addressed by some departments in order to ensure quality radiotherapy treatment of lung cancer.

We identified some variation in the definitions of target volumes in the 4DCT era. However when subsequent volume expansions are taken into account, the resultant PTVs appear similar. It is the terminology and the implementation of the ITV concept which is different between departments rather than the actual PTV volumes to be treated. This is because we have had to adapt published target volume definitions in the era of 4DCT. The ICRU 62 report, published in the 3DCT era, starts off with a GTV to CTV expansion followed by a CTV to ITV expansion.[7] A further expansion is added for PTV. With 4DCT technology, it is easier and more practical to add the internal margin to the GTV (iGTV) first either via automated propagation or by manual contouring of individual respiratory phases or MIP image. A margin added to iGTV to account for subclinical spread then fits the ICRU 62 definition of ITV which incorporates both motion and subclinical spread. In cases of SABR iGTV is identical to ITV but for conventional radiotherapy, ITV will be larger than iGTV. This largely supersedes the need for CTV delineation except for cases where 3DCT is used, breathhold technique is used or for post-operative adjuvant radiotherapy. These issues highlight the need for standard volume definitions and nomenclature for use in lung cancer radiotherapy with 4DCT simulation, until ICRU is updated to address this. (Table 3)

Importantly we found considerable variation in the way in which lung OAR volumes and hence dose volume metrics were calculated in patients having curative radiotherapy for lung cancer. Of concern, between 17%-26% of responses stated that these OAR volumes varied according to individual clinicians rather than being standard across the department. This has the potential to result in error if radiation therapists are having to adjust DVH parameters for interpretation for different clinicians.

We found that the different methodologies for calculating commonly used metrics such as MLD, V20 and V30 resulted in discrepancies that were not trivial and potentially large enough to under- or over-estimate clinical pneumonitis risk. Similar findings have been reported by others when comparing subtractions of GTV and PTV. Wang et al reported that the largest difference was 7.5Gy for MLD and 12.6% for V20[17] whilst Kabolizadeh et al found a 1.9Gy difference in mean MLD and 2.5% difference in mean V20[18]. These differences are magnified with larger tumour volumes.[18] However, both these studies were conducted in the 3DCT era whilst the current study investigates how respiratory motion is being accounted for when calculating lung OAR DVHs.

ESTRO and Australian radiotherapy guidelines recommend “Total lung – GTV” for lung DVH calculations whilst ASTRO guidelines do not comment on this.[12,13,19] In the setting of 4DCT, the definition of GTV is unclear; is it on one phase of the respiratory cycle or all phases? Despite these guidelines, there is variability in practice. This makes it difficult to compare toxicity outcomes between centres and assess whether these outcomes are acceptable compared to published literature. Furthermore, if the same DVH constraints are used based on different lung OAR definitions, the treatment intent could vary for patients whose lung DVH makes them borderline candidates for curative radiotherapy.

DVH analysis in ten consecutive patients showed that there were potentially clinically significant differences in DVH parameters dependent on the volume being subtracted. Similar findings have been noted by Kong et al for patients treated with stereotactic ablative body radiotherapy.[11] This may result in a lung DVH changing from acceptable to unacceptable, if the constraint is the same regardless of volume being subtracted. It is unclear from our survey if DVH constraints were adjusted where volumes larger than the GTV were being subtracted. When using DVHs reported in the literature, clinicians must ensure that the volumes used to calculate these DVHs are identical, or adjust the constraints accordingly.

The effect of different lung volumes from which the iGTV was subtracted was less than that of different tumour volume subtractions. However clinically significant differences were still seen in some patients suggesting a need for better definitions in the era of 4DCT. The most consistent volume to subtract is the GTV as this avoids the differential margins added for CTV and PTV. CTV margins are dependent on clinical interpretation whilst PTV margins are dependent on the technique used and imaging protocol. Therefore these will differ between centres.

For those scanned with 4DCT, we suggest subtracting GTV in all phases of the respiratory cycle (what we suggest is called the internal GTV or iGTV) as this would be consistent for both conventional radiotherapy and SABR (Table 4). Kong et al have also recently recommended this in the setting of lung SABR.[11] However we found minimal difference in DVH parameters between subtraction of the GTV in expiratory phase and the iGTV. We acknowledge that some centres treat lung SABR patients using the mid-ventilation or mid-position scans rather than encompassing the GTV in all phases of the respiratory cycle. However this does not preclude lung DVH calculations based on iGTV subtraction. In the setting of adjuvant radiotherapy, where there is no GTV, we suggest using total lungs alone without any volume subtraction. For 4DCT, we suggest using the lung volumes be defined on the average scan.

This study is limited by the low response rate to the survey. In addition the DVH analysis was limited to a small number of patients. However this analysis was done on a clinical sample of patients simply for illustrative purposes, to show the consequences of the survey findings of different volume calculations for lung DVH calculations.

Conclusion

Radiation oncology practice standards are not being adhered to for lung cancer radiotherapy in a significant number of departments which do not have contouring protocols to guide their treatment. Definition of lung OAR volumes also differs between and within departments. A robust definition for lung OAR volumes applicable to both 3DCT and 4DCT simulation and also for both conventional radiotherapy and SABR is needed. We suggest subtraction of GTV and iGTV for 3DCT and 4DCT simulation respectively. We strongly urge departments treating lung cancer to develop comprehensive departmental contouring and planning protocols for the safe and quality delivery of radiotherapy for this disease. The Cancer Institute NSW eviQ lung cancer radiotherapy protocols will shortly be updated to incorporate the concepts discussed in this paper and can be used as a basis for departmental protocols.[20]

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Figure Captions

Figure 1 – Presence of departmental protocols for different radiotherapy processes (%)

Figure 2 – Mean lung dose (Gy) calculated for different tumour volume subtractions in 10 patients

Figure 3 – V20 (%) calculated for different tumour volume subtractions in 10 patients

Table Captions

Table 1 – Imaging datasets used for delineation of GTV and lung OAR contours from survey responses

Table 2 – Lung OAR volume definitions from survey responses

Table 3 – Suggested volume definitions and standard nomenclature for lung cancer radiotherapy with 4DCT simulation

Table 4 - Suggested volume definitions for Lung OAR DVH calculations

Table 1 – Imaging datasets used for delineation of GTV and lung OAR contours from survey responses

	GTV for conventional radiotherapy (curative) n=27	GTV for stereotactic ablative body radiotherapy n=25	Lung OAR contours n=27
3DCT	4 (15%)	1 (4%)	13 (48%)
Inhale phase of 4DCT	0 (0%)	0 (0%)	0 (0%)
Exhale phase of 4DCT	1 (4%)	1 (4%)	1 (4%)
All phases of 4DCT	8 (30%)	10 (40%)	0 (0%)
Maximum Intensity Projection	5 (19%)	4 (16%)	0 (0%)
Average Intensity Projection	3 (11%)	3 (12%)	10 (37%)
Other or more than one dataset	6 (22%)	6 (24%)	3 (11%)

Table 2 – Lung OAR volume definitions from survey responses

	Conventional radiotherapy (curative) n=27	Stereotactic ablative body radiotherapy n=23	Conventional radiotherapy (adjuvant) n=24
Total lungs	1 (4%)	0 (0%)	10 (42%)
Total lungs - PTV	6 (22%)	6 (26%)	5 (21%)
Total lungs - CTV	2 (7%)	1 (4%)	5 (21%)
Total lungs – iGTV*	6 (22%)	10 (44%)	NA
Total lungs – GTV#	5 (19%)	2 (9%)	NA
Varied according to clinician	7 (26%)	4 (17%)	4 (17%)

*iGTV = GTV in all phases of the respiratory cycle # GTV = GTV in one phase of the respiratory cycle

Table 3 – Suggested volume definitions and standard nomenclature for lung cancer radiotherapy with 4DCT simulation

Volume	Label	Definition
CURATIVE RADIOTHERAPY		
Gross Target Volume*	GTVp GTVn	Gross Target Volume primary Gross Target Volume nodes
	GTVp_EX GTVn_EX	GTVp delineated on exhale phase GTVn delineated on exhale phase
	GTVp_IN GTVn_IN	GTVp delineated on inhale phase GTVn delineated on inhale phase
	GTVp_X% GTVn_X%	GTVp delineated on particular phase of respiratory cycle where X refers to phase GTVn delineated on particular phase of respiratory cycle where X refers to phase
	GTVp_MIP GTVn_MIP	GTVp delineated on Maximal Intensity Projection GTVn delineated on Maximal Intensity Projection
Internal Gross Target Volume	iGTVp iGTVn	Boolean of GTVp in all phases of the respiratory cycle Boolean of GTVn in all phases of the respiratory cycle
Internal Target Volume	ITVp ITVn ITVDose	Expansion of iGTVp to account for subclinical spread (in addition to motion)[#] Expansion of iGTVn to account for subclinical spread (in addition to motion) Addition of ITVp and ITVn
Planning Target Volume	PTVDose	Expansion of ITVDose to account for set-up error
ADJUVANT RADIOTHERAPY		
Clinical Target Volume*	CTV_EX	CTV delineated on exhale phase
	CTV_IN	CTV delineated on inhale phase
	CTV_X%	CTV delineated on particular phase of respiratory cycle where X refers to phase
Internal Target Volume	ITVDose	Boolean of CTV in all phases of the respiratory cycle

Planning Target Volume	PTVDose	Expansion of ITVDose to account for set-up error

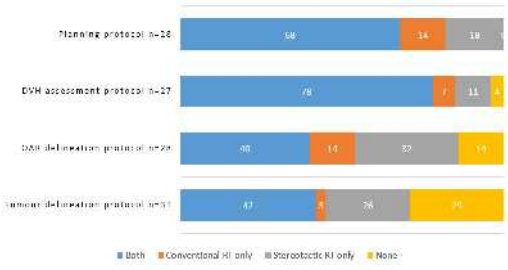
*Multiple definitions of GTV and CTV are given to accommodate different respiratory phases chosen for initial delineation as these may differ between departments

[#]iGTVp=ITVp for SABR

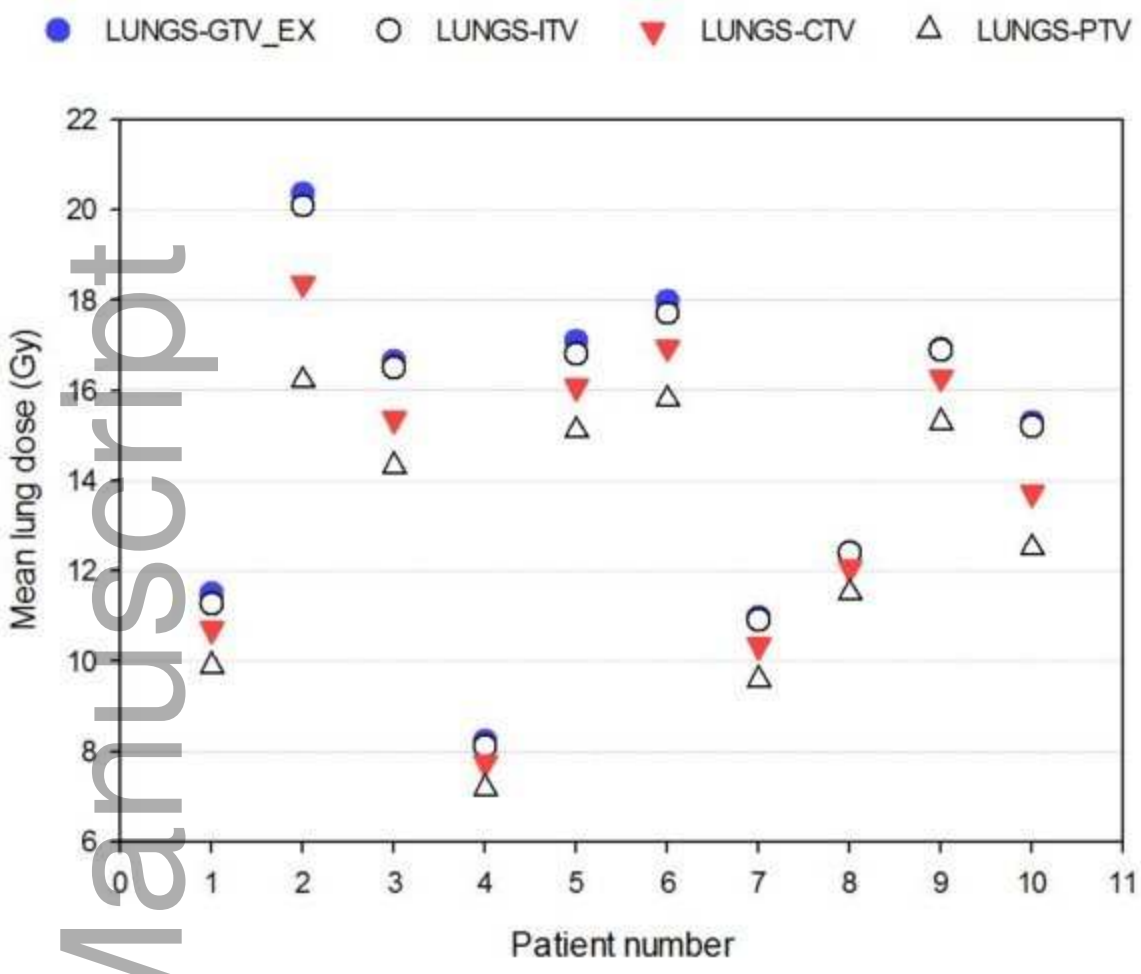
Table 4 – Suggested volume definitions for Lung OAR DVH calculations

Scan	Lung volume delineation	Volume to be subtracted for Lung DVH	
		Curative	Adjuvant
3DCT	Lung windows of 3DCT scan	Total lungs - GTV (primary and nodes)	No volume subtraction
4DCT	Lung windows of average scan	Total lungs - iGTV* (primary and nodes)	No volume subtraction

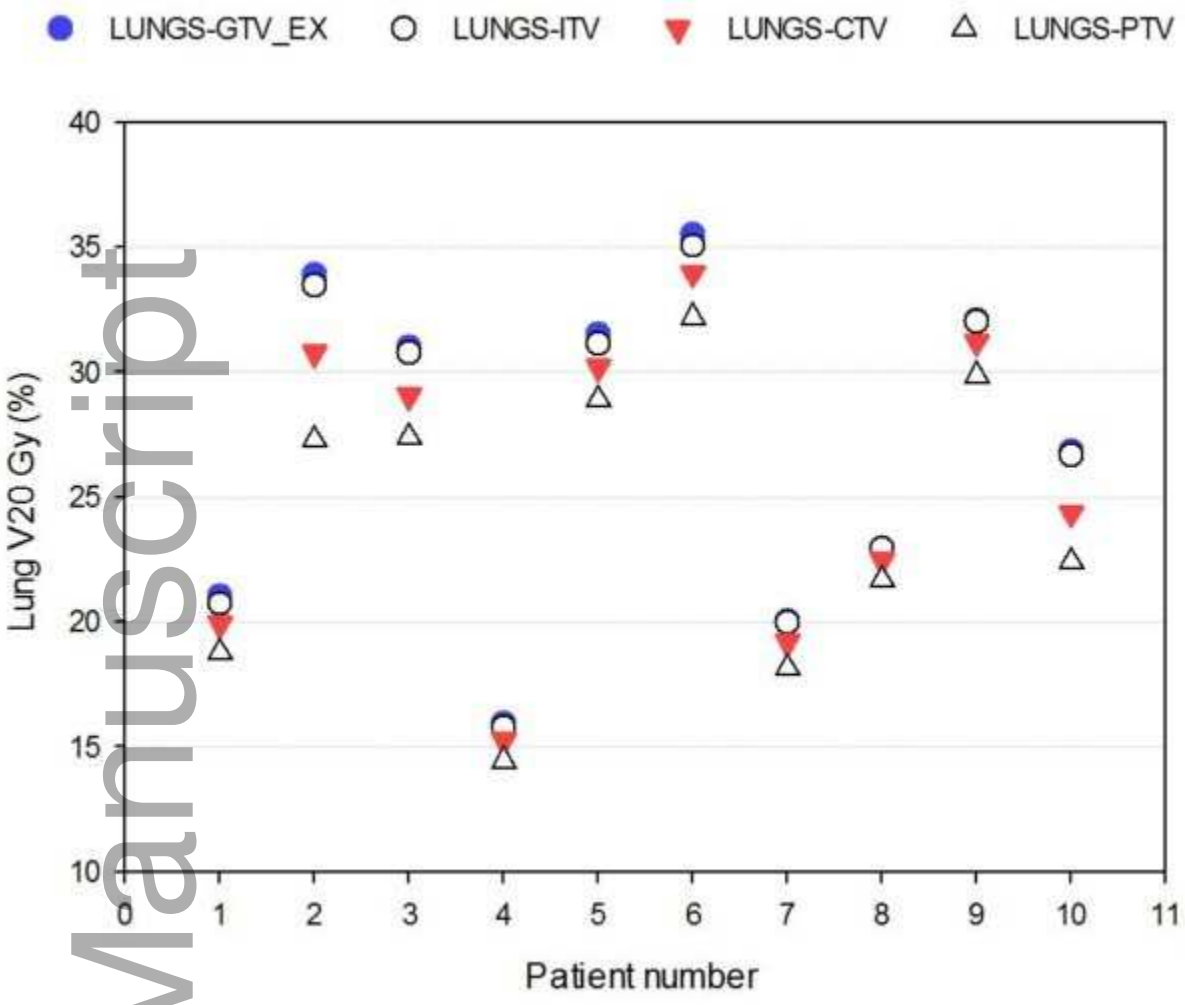
*iGTV=GTV delineated on all phases of respiratory cycle or MIP



ara_12972_f1.tiff



ara_12972_f2.jpg



ara_12972_f3.jpg