CrossRef DOI of original article:

Are Known Lung Dose Limits Valid for All Patients?

Matiello, J.

Received: 1 January 1970 Accepted: 1 January 1970 Published: 1 January 1970

Abstract

Radiotherapy is one of the pillars of the treatment of lung cancer and it can be used as an ablative therapy alone in the early stages of the disease or combined with chemotherapy in more advanced stages (1). Despite its curative role in many settings, radiotherapy is not without side effects. One of the most unwanted side effects is radiation pneumonitis (RP). RP is an inflammatory response resulting from damage to the irradiated lung parenchyma (2) that typically occurs within six months of treatment completion (3). Several factors appear to be associated with the risk of developing RP and its severity, including patient-related, tumor-related, and treatment-related dosimetric factors, as well as tumor size and location (4). Patients receiving chemoradiotherapy or with prior lung resection are also in the group of patients at high risk of developing RP (5-6). However, the analysis of all these variables in the calculating toxicity potentials is uncommonly performed due to the lack of suitable algorithms.

Index terms—

Introduction-Radiotherapy is one of the pillars of the treatment of lung cancer and it can be used as an ablative therapy alone in the early stages of the disease or combined with chemotherapy in more advanced stages (1). Despite its curative role in many settings, radiotherapy is not without side effects. One of the most unwanted side effects is radiation pneumonitis (RP). RP is an inflammatory response resulting from damage to the irradiated lung parenchyma (2) that typically occurs within six months of treatment completion (3).

Several factors appear to be associated with the risk of developing RP and its severity, including patient-related, tumor-related, and treatment-related dosimetric factors, as well as tumor size and location (4). Patients receiving chemoradiotherapy or with prior lung resection are also in the group of patients at high risk of developing RP (5)(6). However, the analysis of all these variables in the calculating toxicity potentials is uncommonly performed due to the lack of suitable algorithms.

1 Introduction

adiotherapy is one of the pillars of the treatment of lung cancer and it can be used as an ablative therapy alone in the early stages of the disease or combined with chemotherapy in more advanced stages (1). Despite its curative role in many settings, radiotherapy is not without side effects. One of the most unwanted side effects is radiation pneumonitis (RP). RP is an inflammatory response resulting from damage to the irradiated lung parenchyma (2) that typically occurs within six months of treatment completion (3).

Several factors appear to be associated with the risk of developing RP and its severity, including patientrelated, tumor-related, and treatment-related dosimetric factors, as well as tumor size and location (4). Patients receiving chemoradiotherapy or with prior lung resection are also in the group of patients at high risk of developing RP (5)(6). However, the analysis of all these variables in the calculating toxicity potentials is uncommonly performed due to the lack of suitable algorithms.

There is essential heterogeneity among patients receiving radiotherapy. Currently, the rate of lung cancer in non-smokers has been increasing synchronously with the increase in the diagnosis of adenocarcinoma and inversely with the diagnosis of squamous cell carcinoma and small cell lung cancer (7). In any case, the number of smokers and patients with previous lung diseases who develop lung cancer is high (8). Such diseases include chronic obstructive bronchopulmonary disease (COBPD) and interstitial lung disease (ILD) and are significant risk factors for cancer. A study published in 2015 demonstrated that patients with COBPD had a higher incidence of pneumonitis associated with consolidation in the irradiated volume (52%) than those without COBPD (16%) (9). The benefits of radiotherapy are well known, but it is essential to pay attention to the particularities of patients to adjust their treatment to minimize pulmonary complications and improve clinical outcomes (10).

Lung densitometry is a method that can differentiate healthy tissue from emphysematous or fibrotic tissue (11,12). This diagnostic method measures lung density and classifies the tissue according to its ability to attenuate X-rays in computed tomography (CT) studies. CT lung density measurements are expressed in Hounsfield units (HU) (13), and the different densities obtained characterize the tissue, reflecting the degree of lung damage. For example, decreased X-ray attenuation occurs in emphysema and cystic lung disease, whereas increased X-ray attenuation occurs in pulmonary fibrosis.

In patients with lung cancer who are candidates for radiotherapy treatment, densitometry provides additional information about the patient's clinical condition (14,15), in addition to the possibility of visually mapping the whole lung tissue and its different densities (figure 1).

2 Materials and Methods

Patients receiving lung stereotactic body radiotherapy (SBRT) for early-stage primary lung tumors (stages I and II) between 2017 and 2022 at Santa Casa de Porto Alegre, Brazil, were selected. Patients with CT scans with a millimetric slice thickness obtained at 120 kV and 80 mAS during forced inspiration were included.

All CT scans were examined for their lung density characteristics. Lung density measurements were made on radiotherapy planning CT scans, obtained with a 64-slice CT scanner (Ingenuity Core 64; Philips Healthcare, Cleveland, OH, USA). The structures of interest were outlined using the Eclipse radiotherapy planning system v15.6 (Varian Medical Systems, Palo Alto, CA, USA). The structures of interest were defined as ”Right Lung,” ”Left Lung,” and ”Lungs” (both lungs drawn as a single structure) and automatically segmented, as were the structures corresponding to the different density ranges to be analyzed.

CT lung density measurements are expressed in HU, a quantitative scale for describing radiodensity divided into 2048 density values, where water is arbitrarily defined to be 0 HU, air is defined as -1000 HU, and bone density as 1000 HU (16). Quantitative indices of emphysema show low attenuation values, corresponding to the proportion of lung volume with attenuation between -1000 and -950 HU (17). Functional lung volume can be measured with attenuation between -950 and -700 HU, and for fibrosis, attenuation values range from -700 to -200 HU (18).

The structures corresponding to the attenuation ranges were obtained using the ”Image Thresholding” tool (figure 2), which allows manual selection of HU values. They were defined as ”Emphysema” for attenuation ranging from -1000 to -950 HU, ”Normal Tissue” (functional lung volume) for attenuation ranging from -949 to -700 HU, and ”Fibrosis” for attenuation ranging from -699 to -200 HU. The attenuation values of -949 HU and -699 HU were used to avoid data duplication. The volumes were then measured and recorded in a table. Given its importance in the clinical and oncological treatment of patients with lung cancer, emphysema was divided into three groups. Emphysema was considered insignificant when it involved less than 5% of the total lung volume, and severe emphysema was defined as involvement more significant than 15% (19). Fibrosis was considered a single group.

Continuous variables are expressed as mean (SD) if normally distributed. Categorical variables are expressed as counts and percentages. Continuous variables were compared using t-tests or the Wilcoxon rank sum test. Data were analyzed in SPSS, version 29.0 (SPSS Inc., Chicago, IL, USA).

3 III.

4 Results

CT data from 39 patients were analyzed. The mean patient age was 71.5 years, and most were female, accounting for 61.5% of the sample. The most common histological type in biopsied patients was adenocarcinoma (62.5%), and the tumor site showed no predilection for any particular lobe. Of the total sample, 26 patients (66.7%) had no or insignificant emphysema (less than 5% of the total lung volume), 7 (17.9%) had 5% to 15% of whole lung tissue with emphysema, being defined as mild-tomoderate emphysema, and 6 (15.4%) had severe emphysema, with greater than 15% of the total lung volume being emphysematous. Tissue with attenuation areas corresponding to fibrosis was found in 7.5% (SE, 1.21).

5 Discussion

There is consensus on the indication of radiotherapy in non-operated patients, both in the early and advanced stages of disease. A 5-year tumor control rate of 90% can be achieved with ablative radiotherapy (20)(21)(22) or hypofractionated radiotherapy for early-stage tumors (23), generally with low toxicity, but not without toxicity, with reports of grade 5 toxicity (24), especially in more centrally located tumors. In the treatment of more advanced tumors, the 5-year local control rate is less than 30% (25), with high rates of severe pneumonitis (grades 3 to 4) affecting one-third of patients when radiotherapy is combined with chemotherapy (26,27), the standard of care for locally advanced tumors (28).

When evaluating radiotherapy planning, dose limits for irradiation of normal lung tissue are tabulated generically. Studies on lung toxicity in three-dimensional treatment suggest that the mean dose to both lungs, excluding tumor volume, should remain below 20 Gy. In comparison, it is prudent to limit the lung volume receiving 20 Gy to 30%, perhaps reaching 35% (V 20Gy ?30-35%) (29), regardless of tumor stage. In ablative radiotherapy, the allowed doses have a different absolute number, but they also treat all patients with dose escalations, regardless of patients' pre-existing lung function and tumor stage. Such doses are V 20Gy <10%, not exceeding the limit of 15%. In addition, the doses must not exceed 12.5 Gy for the critical volume of 1500 cc and 13.5 Gy for 1000 cc (30)(31). The use of V X -based dose analysis ("V" volume of normal lung receiving a dose of "X" Gy) is attractive because this metric can be readily obtained via the dose-volume histogram (DVH). However, as pointed out in the QUANTEC report on pulmonary toxicity, V X cutoffs may not be universal. The percent volume receiving a dose of "X" may depend on the treatment technique and does not allow the inclusion of other toxicity factors associated with the actual final toxicity (32).

In general, in the dose limits suggested in the literature, patients with severe lung disease have their normal tissue considered within the same dose limits as those for patients without any functional changes. The tissue volume considered normal is the tissue without tumor (32,33), that is, excluding the target volume. Therefore, emphysematous or fibrotic areas, known to be entirely non-functional, are regarded as "normal" tissue in the volume.

For lung density analysis, we only included patients with a well-documented inspiration breath-hold technique. For this reason, we chose to analyze patients who would receive SBRT, as this group has a more detailed CT analysis than patients who receive conventional fractionation. It is known, however, that most patients receiving SBRT have clinical conditions unfavorable to surgery, which is still the standard treatment for early-stage tumors (34, 35), whether due to chronic lung disease or other comorbidities. Therefore, our sample has more patients with advanced lung disease than the group of all patients with lung cancer.

Despite the small sample size, the data corresponding to mild-to-moderate emphysema (17.9%) in patients with lung tumors are consistent with data from the literature (36). In the current study, severe emphysema was present in 15.4% of patients, which implies that these patients have limitations, that is, symptoms of their underlying lung disease. When receiving ablative or conventionally fractionated radiotherapy, these patients are more likely to develop clinical and radiological pneumonitis.

6 V.

7 Conclusion

Several studies have demonstrated that accurate quantification of lung density can be helpful in various clinical applications, such as the diagnosis and monitoring of lung diseases, medical procedure planning, and assessment of treatment response. In this study, it was possible to expand the use of tools currently available in the SBRT protocol, such as CT scan at inspiration and resources available in the planning system. The results based on lung densitometry provide essential information about the clinical characteristics of patients who are candidates for radiotherapy treatment, which can be helpful for future research and understanding specific lung conditions, allowing a personalized DVH assessment.

In conclusion, radiation dose-volume effects on the lung play an essential role in the developing pulmonary complications after radiotherapy. A personalized approach, considering risk factors and using advanced techniques, can help minimize these effects and, consequently, improve the quality of life of patients undergoing treatment.

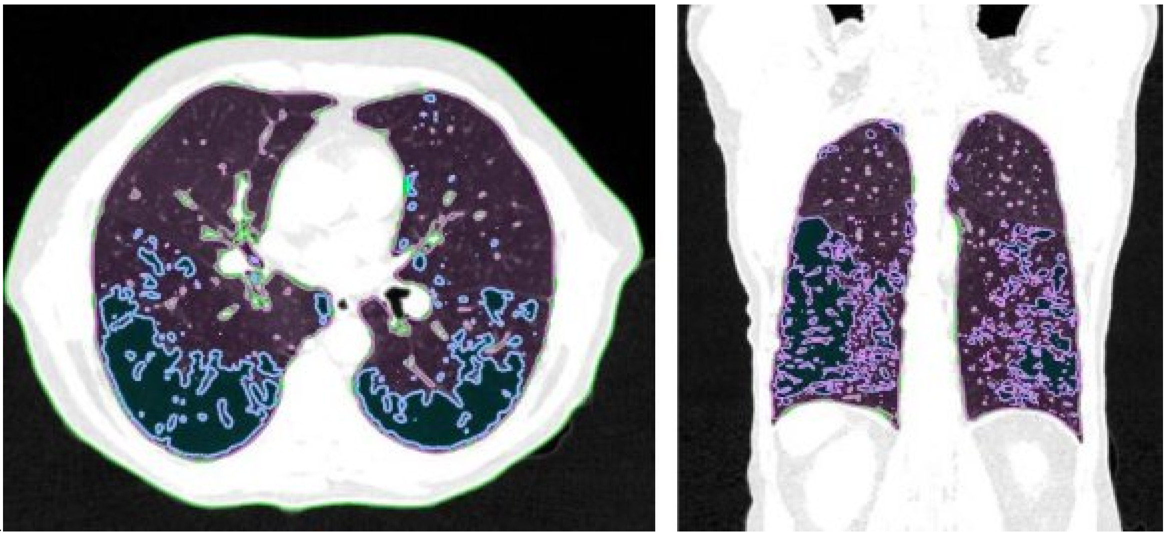
1


Figure 1: Figure 1 :

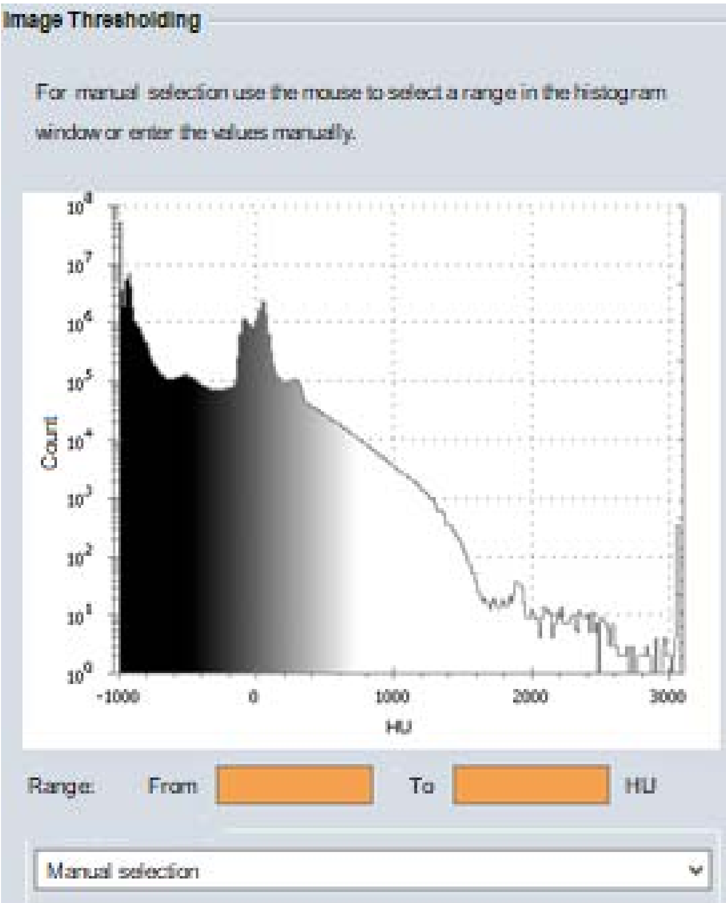
2


Figure 2: Figure 2 :

1

Variable	n=39
Age (years) -mean ± SD [min -max]	71.7 ± 7.9 [55 -87]
Sex -n(%)	
Male	15 (38.5)
Female	24 (61.5)
Staging -n(%)	
Primary tumor with pathological diagnosis	31 (79.5)
No pathological diagnosis, or inconclusive	8 (20.5)
Histological type -n(%)	
Adenocarcinoma	20 (51.3)
Squamous cell carcinoma	12 (30.8)
No biopsy	7 (17.9)
BED (Gy) -mean ± SD [min -max]	152.2 ± 37.2 [85 -180]
Tumor site -n(%)	
RLL	9 (23.1)
LLL	9 (23.1)
RML	1 (2.6)
RUL	10 (25.6)
LUL	10 (25.6)

BED, biologically effective dose; RLL, right lower lobe; LLL, left lower lobe; RML, right middle lobe; RUL, right upper lobe; LUL, left upper lobe.

Figure 3: Table 1 :

2

Percentages	Inspiration Mean ± SE
Emphysema	5.51 ± 1.30
<5%	26 (66.7%)
5% to 15%	7 (17.9%)
>15%	6 (15.4%)
Normal	82.1 ± 1.56
Fibrosis	7.5 ± 1.21
IV.	

Figure 4: Table 2 :

Volume XXIII Issue VIII Version I
D D D D)
(
Medical Research
Global Journal of

Figure 5:

[Radiation Therapy Oncology Group (2011)] , Radiation Therapy Oncology Group . *Philadelphia: RTOG* 2011 Feb 9 -RTOG 0236. (Internet)

[A phase II trial of stereotactic body radiation therapy (SBRT) in the treatment of patients with medically inoperable stage I/II *A phase II trial of stereotactic body radiation therapy (SBRT) in the treatment of patients with medically inoperable stage I/II non-small cell lung cancer. Set*, `http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0236Acess` 2009. 10 julho 2023. Protocol Information.

[Hochhegger ()] 'Acurácia da mensuração do enfisema pulmonar na tomografia computadorizada: pontos importantes'. Bruno Hochhegger . *Radiologia Brasileira* 2010. 43 p. .

[Verma et al. ()] 'Acute and late toxicities of concurrent chemoradiotherapy for locally-advanced non-small cell lung cancer'. Vivek ; Verma , Charles B Simone , Maria Werner-Wasik . *Cancers* 2017. 9 p. 120.

[Balbinot ()] 'Advances in imaging and automated quantification of pulmonary diseases in non-neoplastic diseases'. Fernanda Balbinot . *Lung* 2016. 194 p. .

[Walls ()] 'Clinico-radiological outcomes after radical radiotherapy for lung cancer in patients with interstitial lung disease'. Gerard M Walls . *BJR| Open* 2023. p. 20220049.

[Ryckman ()] 'Correlation of dosimetric factors with the development of symptomatic radiation pneumonitis in stereotactic body radiotherapy'. Jeffrey M Ryckman . *Radiation oncology* 2020. 15 p. .

[Moiseenko ()] 'Dose-volume predictors of radiation pneumonitis after lung stereotactic body radiation therapy (SBRT): Implications for practice and trial design'. Vitali Moiseenko . *Cureus* 2020. 12 (10) .

[Meng ()] 'Excluding PTV from lung volume may better predict radiation pneumonitis for intensity modulated radiation therapy in lung cancer patients'. Yinnan Meng . *Radiation Oncology* 2019. 14 p. .

[Spigel ()] 'Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer'. David R Spigel . *Journal of Clinical Oncology* 2022. 40 p. 1301.

[Kimura ()] 'Functional image-guided radiotherapy planning in respiratory-gated intensitymodulated radiotherapy for lung cancer patients with chronic obstructive pulmonary disease'. Tomoki Kimura . *International Journal of Radiation Oncology* Biology* Physics* 2012. 82. (p. e663-e670)

[Denotter and Schubert ()] 'Hounsfield unit'. Tami D Denotter , Johanna Schubert . *StatPearls Publishing: Treasure Island*, (FL, USA) 2019. (StatPearls)

[Videtic ()] 'Long-term follow-up on NRG Oncology RTOG 0915 (NCCTG N0927): A randomized phase 2 study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer'. Gregory M Videtic . *International Journal of Radiation Oncology* Biology* Physics* 2019. 103 (5) p. .

[Timmerman ()] 'Long-term results of stereotactic body radiation therapy in medically inoperable stage I non-small cell lung cancer'. Robert D Timmerman . *JAMA oncology* 2018. 4 p. .

[Dubin and Griffin ()] 'Lung cancer in non-smokers'. Sarah ; Dubin , Daniel Griffin . *Missouri Medicine* 2020. 117 p. 375.

[Mascalchi et al. ()] 'Lung densitometry: why, how and when'. Mario ; Mascalchi , Gianna ; Camiciottoli , Stefano Diciotti . *Journal of Thoracic Disease* 2017. 9 p. 3319.

[Bakker ()] 'Measuring pulmonary function in COPD using quantitative chest computed tomography analysis'. Jens T Bakker . *European Respiratory Review* 2021. 30.

[Houghton and Mcgarry ()] 'Mechanistic links between COPD and lung cancer'. A Houghton , Mcgarry . *Nature Reviews Cancer* 2013. 13 p. .

[Aupérin ()] 'Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer'. Anne Aupérin . *Database of Abstracts of Reviews of Effects (DARE): Qualityassessed Reviews*, 2010. (Internet)

[Cheng ()] 'Normal lung attenuation distribution and lung volume on computed tomography in a Chinese population'. Ting Cheng . *International journal of chronic obstructive pulmonary disease* 2019. p. .

[Bezjak ()] *NRG ONCOLOGY RTOG 0813 Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for early stage, centrally located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients*, A Bezjak . 2012. Update.

[Hersh ()] 'Paired inspiratory-expiratory chest CT scans to assess for small airways disease in COPD'. Craig P Hersh . *Respiratory research* 2013. 14 p. .

[Palma ()] 'Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis'. David A Palma . *International Journal of Radiation Oncology* Biology* Physics* 2013. 85 p. .

[Bongers ()] 'Predictive parameters of symptomatic radiation pneumonitis following stereotactic or hypofractionated radiotherapy delivered using volumetric modulated arcs'. Eva M Bongers . *Radiotherapy and Oncology* 2013. 109 p. .

[Marks ()] ‘Radiation dose-volume effects in the lung’. Lawrence B Marks . *International Journal of Radiation Oncology* Biology* Physics* 2010. 76 (3) p. .

[Konkol et al. ()] ‘Radiation-induced lung injury-what do we know in the era of modern radiotherapy’. Marek ; Konkol , ?niata?a , ; Pawe? , Piotr Milecki . *Reports of Practical Oncology and Radiotherapy*, 2022. 27 p. .

[Vinod and Hau ()] ‘Radiotherapy treatment for lung cancer: Current status and future directions’. Shalini K Vinod , Eric Hau . *Respirology* 2020. 25 p. .

[Tatsuno ()] ‘Risk factors for radiation pneumonitis after rotating gantry intensitymodulated radiation therapy for lung cancer’. Saori Tatsuno . *Scientific Reports* 2022. 12 p. 590.

[Liu ()] ‘Risk factors for symptomatic radiation pneumonitis after stereotactic body radiation therapy (SBRT) in patients with non-small cell lung cancer’. Yongmei Liu . *Radiotherapy and Oncology* 2021. 156 p. .

[Bezjak ()] ‘Safety and efficacy of a fivefraction stereotactic body radiotherapy schedule for centrally located non-small-cell lung cancer: NRG oncology/RTOG 0813 trial’. Andrea Bezjak . *Journal of Clinical Oncology* 2019. 37 p. 1316.

[Nyman ()] ‘SPACE-a randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC’. Jan Nyman . *Radiotherapy and Oncology* 2016. 121 p. .

[Timmerman ()] ‘Stereotactic body radiation therapy for operable early-stage lung cancer: findings from the NRG oncology RTOG 0618 trial’. Robert D Timmerman . *JAMA oncology* 2018. 4 p. .

[Inoue et al. ()] ‘Stereotactic body radiotherapy for Stage I lung cancer with chronic obstrutive pulmonar disease: special reference to survival and radiation-induced pneumonitis’. Toshihiko ; Inoue , Shiomi , ; Hiroya , Ryoong-Jin Oh . *Journal of Radiation Research* 2015. 56 p. .

[Coxson ()] *The presence and progression of emphysema in COPD as determined by CT scanning and biomarker expression: a prospective analysis from the ECLIPSE study. The lancet Respiratory medicine*, Harvey O Coxson . 2013. 1 p. .