RESEARCH ARTICLE

Editorial Process: Submission:02/01/2025 Acceptance:09/15/2025 Published:09/12/2025

Acute Pulmonary Toxicity and Quality of Life in Curative Intent Radiotherapy of Thoracic Tumours

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Abstract

Purpose: This study evaluates the acute effects of radiation on the lung, its dosimetry, and its impact on lung subvolumes and quality of life. **Methods:** This is a prospective study of patients with thoracic and breast tumours undergoing radical intent radiotherapy. Patients were treated with radiation as per standard practice for the disease site. The clinical assessment of pulmonary toxicity was performed as per Radiation Therapy Oncology Group (RTOG) at the end of four months of radiation. The lung sub-volumes were delineated, and dosimetry was recorded. The quality of life was assessed pre- and post-RT (at four months) using the European Organization for Research and Treatment of Cancer (EORTC) QLQ C30 3.0 questionnaire. **Results:** Thirty patients were recruited in this study. Only one patient out of a total of thirty patients (3.3%) in this cohort showed symptoms of pulmonary toxicity at the end of four months of completion of radiation. There is a positive correlation between the dose prescribed and the dose received by the lung subvolumes. As the dose prescribed increases, the dose received by the lung sub volumes also increases. However, only a few parameters are statistically significant. Quality of life significantly improved post-radiation, particularly in global health status and physical functioning. **Conclusions:** The present study shows a low incidence of acute lung toxicity post-radiation. The dose received by lung sub volumes increases with the prescribed dose. Quality of life improved following radiation and was not correlated with dose.

Keywords: Radiation pneumonitis- Radiation-induced lung injury- pulmonary toxicity- Quality of life

Asian Pac J Cancer Prev, **26 (9)**, 3291-3298

Introduction

Malignancies of the thorax are a heterogeneous group that includes lung cancers, breast cancer, oesophagal cancer and mediastinal tumours. As per GLOBOCAN 2022 data, carcinomas of the lung and breast (female population) are the most commonly occurring cancers worldwide [1]. The incidence of carcinoma of the lung is approximately 12.4%, and the incidence of carcinoma of the breast is approximately 11.6% of total new cases [1]. The incidence of other cancers is low; carcinoma of the oesophagus is approximately 2.6%, while Hodgkin's lymphoma is approximately 0.4% of total new cases [1].

All thoracic cancers require multimodality treatment, with radiation being an essential component. For stage III lung cancers which are inoperable, chemoradiation is the standard of care [2]. For the treatment of carcinoma breast, adjuvant radiotherapy (RT) is part of breast conservation therapy (BCS) and is used to target the microscopic disease within the breast with the aim of locoregional disease control [3]. Post-operative RT in patients with advanced-stage breast cancer is indicated if T3 or T4 tumor, N2 or N3 disease and/or node positivity following neoadjuvant chemotherapy [2]. The preferred modality of treatment in carcinoma esophagus for inoperable or unfit patients or cervical tumours is definitive chemoradiation with close observation [4]. The standard of care for limited-stage Hodgkin's lymphoma is two or three cycles of doxorubicin/bleomycin/vinblastine/ dacarbazine (ABVD) followed by conventionally fractionated RT [2, 5, 6].

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Radiation is given with a dose of either 20 or 30 Gy involved-field radiotherapy (IFRT).

The lung is a critical organ at risk while delivering radiation to the thorax. The incidence of symptomatic radiation pneumonitis (RP) has been reported to be 1% to 34% [7]. The incidence of RP in patients with carcinoma oesophagus is 6.6% [8]. In Hodgkin lymphoma, where patients are treated with mediastinal VMAT radiation combined with chemotherapy, a 10% risk of developing radiation pneumonitis is present [8]. The breast cancer patients with post-mastectomy RT have a low incidence of pneumonitis with a prevalence of 1.8% [8]. Acute RP in patients receiving thoracic radiation will manifest as dyspnea, nonproductive cough, pleuritic chest pain, fever, rales, and a consistent radiographic picture not explained by other abnormalities, such as pneumonia or pulmonary embolus [9]. Delayed radiation fibrosis occurs after many months after radiation and is often clinically asymptomatic. It is observed that RP occurs 8-16 weeks after single-dose or fractionated therapy. The preexisting lung diseases like chronic obstructive lung disease or interstitial lung disease in patients receiving radiation are common and have a critical role in radiation pneumonitis [10].

There is no absolute linear correlation between the risk of RP and Mean Lung Dose (MLD), but the risk is higher with increasing dose [9]. The risk of clinically detectable radiation-induced lung injury with a MLD of 20 Gy was 20%, and 30 Gy was 40% [9]. The larger values of V30 and MLD are associated with a higher risk of lung toxicities [11]. Chargari et al. [12] observed correlation between risk of radiation pneumonitis and lung dosimetry. Risk of radiation pneumonitis is almost nil when V20 Gy <8%. Similarly, risk of radiation pneumonitis is marginal when the V30 Gy < 18%. But when V30 ≥ 18%, the risk of lung toxicity becomes 24% [12].

This study aimed to evaluate the acute effects of radiation on the lung, its dosimetry, and its impact on lung subvolumes. We report the acute toxicity of thoracic radiation, the dose to lung volumes, and its correlation with quality of life (QOL).

Materials and Methods

This is a substudy of a larger prospective study titled "Assessing the impact of radiation dose exposure to lung and heart on effort tolerance." Institutional ethics committee approval was obtained.

Patients who planned for definitive or adjuvant thoracic radiotherapy involving lung in radiation portal, adequate baseline hematocrit, an estimated life expectancy of at least 12 months, and were willing to participate in the study were recruited. Patients with a Karnofsky performance status (KPS) score of <70, treated with stereotactic body radiotherapy (SBRT), presence of comorbidities such as chronic lung disease, cardiac disease, anaemia at presentation, chronic kidney disease, peripheral neuropathy or disabilities in ambulation that might interfere with the conduct of the physical assessments, baseline impairment in respiratory or cardiac function as an indirect result of the tumour, like lobar/pulmonary collapse secondary to obstructing tumour, pleural or pericardial effusion, presence of lung or cardiac metastases, and patient undergoing surgery for oesophageal or lung cancer were excluded from the study.

Patients meeting the eligibility criteria were enrolled in the study after obtaining written informed consent. All patients were discussed in the multidisciplinary tumour board and received radiotherapy as a part of their multimodality treatment. According to the site, the radiation was delivered as per standard institutional practice. The immobilization for treatment was done per the practice specific to the tumour site. All patients underwent computed tomography (CT) simulation followed by volume delineation, and treatment planning was done as per the standard practice by the radiation oncologist and the medical physicist. The lung subvolumes were delineated along with the organs at risk (OARs) and target volumes. The lung subvolumes were delineated anatomically as well as in relation to the central bronchial tree, as shown in Figures 1 and 2. In the right lung, the upper lobe, middle lobe and lower lobe were delineated as per division by horizontal and oblique fissures. Similarly, in the left lung, the upper and lower lobes were delineated with respect to the oblique fissure. The central bronchial tree was first delineated to demarcate the central and peripheral lungs. Then, a further 2cm margin was created circumferentially to obtain the central lung. This was cropped from air and other anatomical boundaries. The peripheral lung constituted the contours of both lungs, excluding the central lung.

The assessment and follow-up were done four months after the completion of radiation. Patients were assessed clinically for pulmonary toxicities using the Radiation Therapy Oncology Group (RTOG) pulmonary toxicity scale and essential clinical respiratory system examination. The QOL was assessed using the EORTC (The European Organization for Research and Treatment of Cancer) QLQ C30 3.0 questionnaire at baseline and 4-month follow-up. The scores were calculated per the EORTC scoring manual. Patients' demographic factors (age, gender, comorbidities) were recorded from their medical records. The dosimetry data of the lung and its lung subvolumes was retrieved from the Monaco planning system version 5.11.03.

Demographic variables were presented using descriptive statistics like mean, median, standard deviation (SD), and Interquartile Range (IQR). Pearson's correlation correlates the prescribed dose with the dose of lung subvolumes. The Wilcoxon sign rank test compares quality of life pre- and post-radiation. A two-tailed p-value was calculated to determine the statistical significance of the results, with a value less than 0.05 being significant.

Results

This study was conducted from August 2022 to June 2024. We considered a total of 30 patients with thoracic and breast tumours undergoing radical intent radiotherapy by convenient sampling. The mean age for the cohort was 51 years, with an SD of 11.5. Table 1 shows the demographic details. Tumour stratification is as follows:

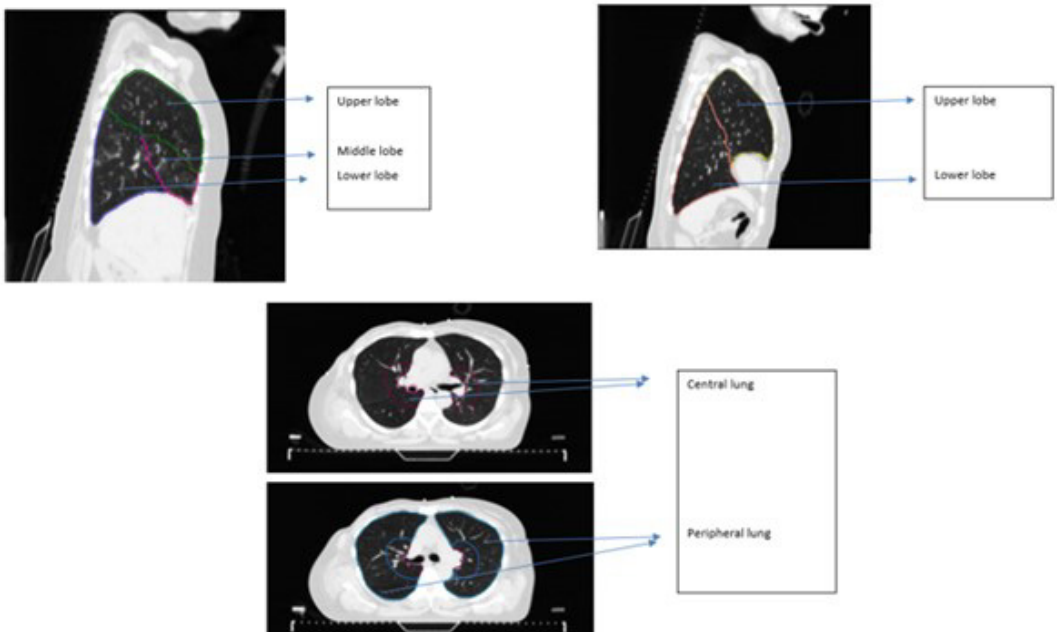
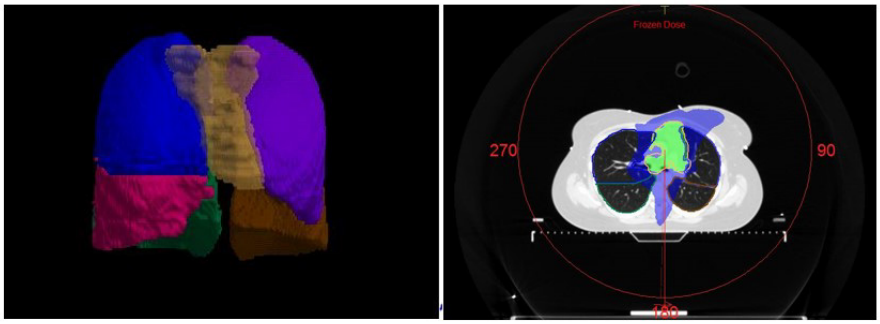


Figure 1. Delineation of Lung Sub Volumes



A B

Figure 2. A. Geographical correlation of PTV and lung sub volumes in a case of mediastinal tumour, B. VMAT plan for a case of mediastinal tumour with dose wash.

Apart from 25 (83%), carcinoma breast patients, the other diagnoses were Carcinoma oesophagus 10%, (n=3), Carcinoma lung 3.3% (n=1) and Hodgkin's lymphoma-bulky stage (Mediastinal tumour) 3.3% (n=1).

The staging parameters are elaborated in Table 2. One patient was oligometastatic (n=1) to sternum from breast cancer and the sternum was treated one month after receiving radiation to the breast with SBRT. The MLD was left at 0.7 Gy and right at 0.8 Gy. As the contribution from SBRT to lung doses was insignificant, the patient was not excluded from the study. All patients were treated with multimodality treatment (Table 3). The RT doses prescribed for carcinoma breast were 40 Gy in 15 fractions in 22 patients, 42.5 Gy in 16 fractions in two patients and 26 Gy in 5 fractions in one patient. The site of treatment was breast/ chest wall and supraclavicular region in 23 patients. The boost dose received for intact breast was 12.5 Gy in 5 fractions or 10 Gy in 5 fractions. The radiation dose delivered for carcinoma oesophagus patients was 52.4 Gy in 20 fractions, 63 Gy in 28 fractions and 60 Gy in 30 fractions in one patient each. The patient diagnosed with Hodgkin's lymphoma was treated with 30 Gy in 15 fractions over three weeks, while the one with carcinoma lung was treated with 60 Gy in 30 fractions over six weeks. Of the 30 patients, 11 were treated using the Volumetric modulated arc therapy (VMAT) technique, and 19 were treated using the three-dimensional conformal radiotherapy (3DCRT) technique. Boost dose in Carcinoma breast cases was not considered during the statistical calculations, as boost dose had a minimal impact on the overall lung doses when calculating lung dosimetry.

Lung dosimetry

The mean V12 for ipsilateral lung was 21.9 % (SD 8.9%). For the entire cohort, the V20 dose was 9.5% (SD 11%) for the right lung and 8.5% (SD 8.7%) for the left lung.

Pulmonary toxicity

Only one patient (3.3%) was found to have Grade 1 pulmonary toxicity at four months of completion of thoracic radiation. The patient was treated for breast

Table 1. Demographics Variables of the Cohort

Parameter	Percentage %
Gender	
Female	90
Male	10
Comorbidities	
Hypertension	10
Ischemic Heart disease	6.60
Diabetes mellitus	6.60
Hypothyroidism	3.30
Bronchial asthma	3.30
No comorbidities	73
Habits	
Smoking	0
Alcohol	3.30
Tobacco chewing	0
Betel nut chewing	3.30
No habits	93
Diagnoses	**No. of patients**
Carcinoma breast	25
Carcinoma esophagus	3
Carcinoma lung	1
Mediastinal tumour (Hodgkins lymphoma)	1
Site of esophageal lesion	
Upper	2
Lower	1
Laterality of carcinoma breast	
Right	12
Left	13
Location of breast lesion	
Upper outer quadrant	19
Upper inner quadrant	5
Lower inner quadrant	1
Lower outer quadrant	1
Central	1

Table 2. The Tumour Node and Metastases Staging of the Cohort

T staging carcinoma breast	
ypT0	4
ypT1/pT1	7
ypT2/pT2	12
ypT3/pT3	2
N staging carcinoma breast	
Nx	4%
N0	24%
N1	48%
N2	16%
N3	8%
T staging carcinoma esophagus	
cT1	0
cT2	0
cT3	3
N staging carcinoma esophagus	
N0	1
N1	0
N2	2
M staging of entire cohort	
Non-metastatic	29
Oligometastatic	1
Distant metastasis	0

cancer and manifested features of a dry cough, which was relieved with symptomatic medication. The patient underwent chemotherapy with four cycles of Doxorubicin and Cyclophosphamide and 12 cycles of Paclitaxel. She received adjuvant RT to the whole breast, supraclavicular and internal mammary nodal (IMN) region with a dose of 40 Gy in 15 fractions followed by a boost dose to the post-op bed of ten Gy in five fractions over one week with VMAT technique. The V12 for ipsilateral lung for this patient was 47.8%. The mean lung doses for this

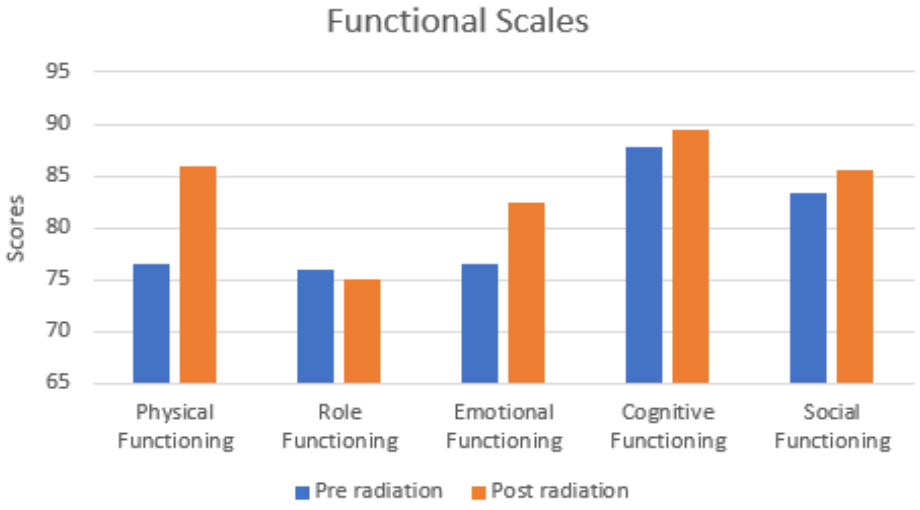


Figure 3. Functional Scales Pre and Post Radiation

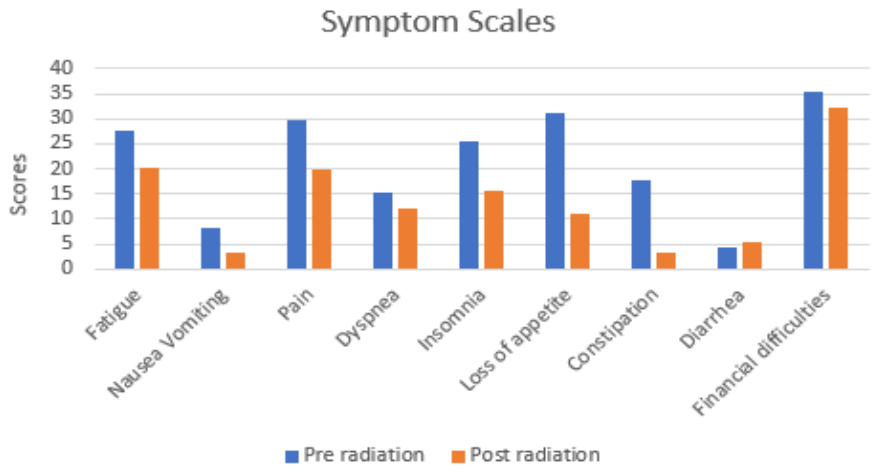


Figure 4. Symptom Scales Pre and Post Radiation

patient were 13.02 Gy to the right lung and 4.06 Gy to the left lung.

Correlation of dose and lung sub-volumes

A positive correlation exists between the total dose prescribed and the dose received by the lung subvolumes. As the dose prescribed increases, the dose received by the lung sub volumes also increases. But only a few are statistically significant. For this cohort, the correlation of dose prescribed and lung subvolumes is statistically significant for V5 right lung (p=0.007) and left lung(p=0.013), V10 right (p=0.003) and left lung (p=0.013), V20 right lung (p=0.017), V30 right lung(p=0.014), V40 right (p=0.004) and left lung (p<0.001), MLD right lung (p=0.003), MLD right lung upper lobe(p=0.003), MLD central (p=0.002) and peripheral lung (p<0.001) and MLD left lung lower lobe (p<0.001).

Correlation of dose and lung subvolumes for Carcinoma breast cohort

For the breast cohort in this study, there is a negative correlation between the dose prescribed and dose to lung subvolumes for V5 right lung, V20 right lung and MLD right lung middle lobe. All the other lung sub-volumes positively correlate with the prescribed dose, and none are statistically significant.

Table 3. The Treatment Details of the Cohort

Treatment	No. of patients
Breast conservation surgery	10
Modified Radical mastectomy	15
Chemotherapy drug	
AC	21
Taxane	22
Trastuzumab	7
Platinum	3
Pemtrexed	1
Geftinib	1
Doxorubicin	1
Etoposide	1
Vinblastine	1
Dacarbazine	1
Epirubicin	1
No chemotherapy	2
Hormone therapy (Tamoxifen/ Aromatase Inhibitor)	18

Quality of life for cohort

The global health status (p=0.004) and physical functioning (p=0.042) significantly improved following radiation. The scores of symptoms like fatigue, nausea and vomiting, pain, dyspnea, insomnia, loss of appetite and constipation decreased post radiation. Out of these symptoms, decrease in only loss of appetite was statistically significant (p=0.017). The financial difficulty scores also decreased post radiation. The functional and symptom scales are depicted in Figure 3 and 4. There was no significant correlation of the quality of life post radiation with lung sub volumes.

Discussion

This study evaluated the acute pulmonary toxicity among cancer patients receiving thoracic radiation and only 3.3% developed toxicity. The lung sub volumes were delineated and showed increase in dose in few regions. The global and physical functioning domains of quality of life improved significantly following radiation.

The one patient (3.3%) who was found to have clinically Grade 1 of pulmonary toxicity had a high MLD and V20. An MLD of 13.5 Gy or greater and a V20 of 33.5% or greater were identified as risk factors for developing acute RP [13]. The IMN radiation leads to an increased risk of lung injury [14]. There is no absolute linear correlation between the risk of ARP and MLD, but the risk is more pronounced with increasing MLD [9]. It has been observed that the hypofractionated VMAT technique for RT of breast cancer results in less acute toxicity as compared to the conventional 3DCRT technique [15]. Another study, which compares dosimetric data of 3D-CRT vs. Intensity-modulated radiotherapy

(IMRT) vs. VMAT in Left-Sided Breast Cancer patients, shows that left lung V20 dose was highest in IMRT (36.64±4.45) followed by 3D-CRT (34.80±2.24) and the most negligible value in VMAT (33.03±4.20) [16].

The rates of acute pulmonary toxicity in breast cancer are low. In the HYPORT study, only two patients out of 135 patients (1.4%) experienced Gr I pulmonary toxicity in the experimental arm and only one patient out of 136 patients (0.7%) experienced Gr I pulmonary toxicity in the control arm [17]. In Maiti et al. [18] the frequency of lung toxicity occurred in both arms: 3·9% in the conventional arm and 3·3% in the hypofractionated arm. Similarly, in the START B trial, symptomatic lung fibrosis was reported in 1.4% of patients and confirmed in 0.3% of patients. In Yadav et al. [19] 99.8% of patients did not develop radiation pneumonitis, and only 0.2% of patients were seen to develop grade 3 radiation pneumonitis. The rate in this study was 3.3%, in line with the literature.

Ay Eren et al. [20] looked at changes in respiratory symptoms and QOL in lung cancer patients and inferred that radiation offered palliation of respiratory symptoms and improved QOL. Chen et al. [21] analysed the QOL in breast cancer patients post-radiation. They reported no significant difference in the fatigue scores, sleep disturbance, physical function, activities and pain, although anxiety and depression were improved post-radiation. Versmessen et al. [22] showed that hypofractionated tomotherapy patients had a better improvement in global health status and role- and cognitive-functioning, and a faster recovery from fatigue, than conventional RT patients. Similarly, in our study, overall quality of life improved post-radiation for the entire cohort.

Chemotherapy has also shown some relation with respect to pulmonary toxicity for cancer treatment. Some drugs significantly increase the risk of toxicities because they increase normal tissue radiosensitivity [13]. Taghian et al shows 14.3% patients experienced radiation pneumonitis who received concurrent paclitaxel and RT [23]. Percentage of lung volume irradiated in the patients who developed RP in the cohort receiving RT and paclitaxel concurrently was 14% whereas it was only 26.3% in the cohort receiving sequential RT and paclitaxel [23]. Patients who did not develop RP, approximately 22% of the lung volume were irradiated in both cohorts. Thus we can infer that, with concurrent chemotherapy, reduction in the volume of the lung radiated, does not affect the risk of incidence of lung injury. Also, we can deduce that paclitaxel could be the dominant risk factor for the development of RP [23]. Taxane based chemotherapy when used sequentially along with radiation has low effect on lung toxicities [7]. The patient who developed grade I pulmonary toxicity in our cohort, underwent chemotherapy with 4 cycles of Doxorubicin and Cyclophosphamide and 12 cycles of Paclitaxel followed by surgery and subsequently radiation.

Delayed radiation fibrosis occurs after many months after radiation and is often clinically asymptomatic. Late pneumonia occurs after approximately 6 months at the end of thoracic radiation [12]. It is a constant on radiological imaging. This phase depicts the replacement of the inflammatory infiltrate by fibrosis and obliteration of the capillaries causing chronic ischemia [12]. Late radiation pneumonitis is a dose limiting complication and severely impacts quality of life. In very rare cases it can also be lethal.

This is a prospective study evaluating acute toxicity and part of a more extensive study looking at the impact of a 6-minute walk test on lung toxicity. We delineated the lung subvolumes, assessed dosimetry, and tried to correlate them with toxicity and QOL. To our knowledge, no other study in the literature has evaluated the doses received by the lung subvolumes or their correlation with toxicity and QOL.

There are a few limitations of this study. This is a pilot study and the sample size is too small to draw meaningful conclusions about pulmonary toxicity or its correlation with lung sub-volumes. However, we were able to delineate lung sub volumes and estimate dosimetry to these regions. This study correlated lung sub volume dosimetry with toxicity and QOL at time point of 4 months, which was insignificant. It will be more meaningful to compare lung sub volume for dosimetry with incidence of lung toxicity and QOL parameters at 6 months, 1 year and 2 years. The latter time points are likely to show clinical radiation pneumonitis or radiological changes which may correlate with lung sub volumes. The low sample size limits the ability of us to derive meaningful results. However, this may be significant in a larger cohort and impact the volume loss and function post-radiotherapy along with late toxicity. The present study shows a low incidence of acute lung toxicity (3.3%), particularly in the 3DCRT era, where organ doses are routinely evaluated. The lack of a control group and confounding by chemotherapy-induced lung toxicity is another limitation of the study. Patient with thoracic malignancies receive either neoadjuvant or concurrent chemotherapy and this could impact lung toxicity. In the present study, since only one patient developed toxicity, we did not perform a multivariate analysis.

In conclusion,the present study was to evaluate the acute toxicity of thoracic radiation and its impact on dosimetry to lung subvolumes and quality of life, and we found low acute pulmonary toxicity. A positive correlation exists between the dose prescribed and the dose received by the lung subvolumes. Quality of life significantly improved in global health status and physical functioning following radiation.

Author Contribution Statement

Aakriti Bhardwaj1: Designing article, intellectual inputs, approve for publication, agree for accountability. Jyothi Nagesh : Designing article, intellectual inputs, approve for publication, agree for accountability. Lahari U: Designing article, intellectual inputs, approve for publication, agree for accountability. Srinivasan Vijayakumar1: Designing article, intellectual inputs, approve for publication, agree for accountability. Anshul Singh: Designing article, intellectual inputs, approve for publication, agree for accountability. Umesh Velu: Designing article, intellectual inputs,

approve for publication, agree for accountability. Ankita Mehta: Designing article, intellectual inputs, approve for publication, agree for accountability. Jayashree NP: Designing article, intellectual inputs, approve for publication, agree for accountability. Srinidhi G Chandraguthi: Designing article, intellectual inputs, approve for publication, agree for accountability. Sarath S Nair: Designing article, intellectual inputs, approve for publication, agree for accountability. Shreekripa: Designing article, intellectual inputs, approve for publication, agree for accountability. Shambhavi C: Designing article, intellectual inputs, approve for publication, agree for accountability. Rechal Nisha Dsouza: Designing article, intellectual inputs, approve for publication, agree for accountability. Krishna Sharan: Concept, intellectual inputs, approve for publication, agree for accountability. Shirley Lewis: Designing article, intellectual inputs, approve for publication, agree for accountability.

Acknowledgements

None.

CTRI registration

CTRI/2022/08/045087

IEC no.

IEC Approval No. 837/2021 obtained on14th May 2022 by The Ethics Committee: Kasturba Medical College and Kasturba Hospital Institutional Ethics Committee. All participants who are a part of the study have given a written informed consent to participate in the study.

Presentations

Poster Presentation at AROICON 2024.

Conflicts of interest

None

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