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Original Research

Precision radiotherapy by SPECT lung functional imaging in NSCLC

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Abstract

Background: Single Photon Emission Computed Tomography (SPECT) could be used to avoid the non-affected perfusion areas in patients with non-small-cell lung cancer (NSCLC) and to potentially reduce lung toxicity. The aim of this study is to compare dosimetric differences between two different 3D-conformal treatment plans, with and without CT/SPECT contribution. **Methods**: Simulation Computed tomography (CT) scans were accurately co-registered with SPECT scans and three different areas, based on SPECT intensity perfusion, were contoured: low perfusion (LP), medium perfusion (MP) and high perfusion (HP). Two different 3D-conformal plans, with co-planar and nonco-planar fields, were generated; one without SPECT information (anatomic plan), and one using the perfusion area identified with functional imaging (functional plan). **Results**: 9 patients were planned and a total of 18 plans were available for analysis. Anatomical and functional plans resulted in comparable planning target volume (PTV) coverage. In the functional plans, a significant reduction of dose in high perfusion areas was reported. The reduction of HP-V20 Gy values ranged from 15% to 8% (p = 0.046), the ipsiHP-V20 Gy from 38% to 22% (p = 0.028) and ipsiHP-Dmean reduction from 16 Gy to 12 Gy (p = 0.039). No significant differences in other organs at risk (OARs) metrics were reported between anatomical and functional plans. **Conclusions**: Despite the few cases reported, the strength of our study lies in the reported benefit of functional lung information in 3D conformal radiation planning, without compromising target coverage or worsening dose distribution to the OARs. There is an urgent need for prospective clinical and randomized trials in order to define the role of lung functional imaging in reducing toxicity in clinical practice.

Keywords: pecision medicine; functional imaging; NSCLC; radiotherapy

1. Introduction

Concurrent chemoradiation plays a key role in treatment of locally advanced non-small-cell lung cancer (NSCLC), both as radical treatment in inoperable patients, as well as induction therapy for resectable disease [1–5]. Radiation pneumonitis (RP) is one of the most serious adverse events occurring during and after chemoradiation. In patients treated with conformal radiation therapy (3D-CRT) G3 or higher, pneumonitis is reported in the range of 8%–11% [6,7]. The incidence of RP is due to multiple factors, such as the patient's clinical condition and treatment-related modalities. Several studies have previously evaluated the role of dosimetric predictors as a guide to reducing the incidence of RP [8,9].

Dosimetric constraints, traditionally used for validation of the radiotherapy (RT) plans, refer to both lungs as a single functional unit, without taking into account the possible differences between the doses to the lung where the primary tumor is located (ipsilateral lung, IL), and the contralateral lung. Ipsilateral lung volume receiving >20 Gy is a dose constraint that should be considered in patients treated with concurrent chemoradiation [10].

Radiation technique influences the rate of RP. In the secondary analysis of the radiation therapy oncology group (RTOG) 0617 trial, intensity-modulated radiation therapy (IMRT) led to a statistically significant reduction of G3 lung toxicity in comparison with three-dimensional conformal radiotherapy (3DCRT) [11]. Adaptive radiotherapy, which modulates dose distribution according to the shape and dimension of the tumor changes during treatment, can also contribute to reducing RP [12]. SPECT provides information on the distribution of blood flow and on the perfused areas, which could coincide with the functional sites. The rationale for integrating functional imaging into treatment planning is to adapt dose distribution while sparing the functional lung areas in order to personalize treatment and reduce toxicity. Recently a systematic review and meta-analysis on the role of functional lung imaging has been reported [13], which highlighted two key points: functional lung dose metrics as predictor of RP; and the potential benefits of optimizing radiation therapy plans sparing functional lung areas. A significant heterogeneity in the definition of functional lung and in reporting data were reported by the studies, thereby emphasizing the need for a shared approach. A further recommendation for future functional

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lung sparing trials is the need to take into consideration the potential detriment to surrounding organs (heart, oesophagus, *etc*.) resulting from optimization of functional lung parameters. Associations between heart dose metrics and survival have indeed been reported [14], but current data cannot exclude that too high lung parenchyma dose as such also could lead to early mortality events. Subsequently, avoiding functional lung regions should not be at the expense of increased dose to other organs at risk (OARs). In literature, only studies using IMRT/VMAT techniques reported both the benefit of functional plans in lung dose parameters, as well as the absence of a detrimental effect on other OARs [15–17]. It is not clear, however, whether lung functional imaging also led to a similar benefit with 3D-CRT, which still represents a commonly used approach in most radiation oncology departments.

The aim of the present study is to investigate the contribution of lung functional imaging to an optimized 3D-CRT treatment planning, and its impact on the other thoracic OARs dosimetric parameters.

2. Materials and methods

2.1 Patient selection criteria

This is an observational dosimetric study in NSCLC patients treated with concurrent chemoradiation with 3D-CRT, who underwent SPECT prior to radiotherapy. 65 clinical records of patients with LA-NSCLC treated in the course of 1 year were reviewed, and patients with the following criteria were selected:

SPECT imaging performed within 7 days from the start of RT; SPECT imaging reported by a single nuclear medicine physician (to limit interpersonal variation of imaging interpretation); neoadjuvant chemoradiation; 3D-CRT technique.

2.2 SPECT imaging details

9 patients were identified and a functional plan was performed in line with the lung functional contoured areas identified by SPECT/CT perfusional scans, performed using the siemens symbia intevo tomograph (symbia intevo; siemens healthcare s.r.l., Milan, Italy) after an intravenous injection of 148 MBq of 99mTc-labeled macro-aggregated albumin, using low energy high resolution collimators. Projections were acquired with step and shoot method at discrete 3 angular intervals with each camera head rotating through 180 for a total of 60 views (30 s). Images were captured with a 128 $\times$ 128 matrix and a zoom factor of 1.00. All scans were carried out with free breathing and had sufficient coverage to include the total lung volume. The CT and SPECT scans were co-registered for the purpose of attenuation correction and a more precise anatomical localization of scintigraphy findings.

As also reported in literature, we defined a highly functional lung as the 70% threshold of maximum perfusion [18].

2.3 Radiotherapy details

2.3.1 Contouring

Functional lung volumes were classified into three groups according to their relative tracer uptake in SPECT/CT images: low perfusion (LP) (0%–40%), medium perfusion (MP) (40%–70%) and high perfusion (HP) (70%–100%) areas. Radiotherapy planning CT scans were acquired using Toshiba Aquilion LB (v. TSX 201A, toshiba medical systems corporation, Otawara, Japan) with slice thickness of 3 mm. 18F-FDG PET/CT images were used to define the gross tumor volume (GTV) with the algorithm proposed by Peeters *et al*. [19]. Four-dimensional CT (4D-CT) scans were acquired and targets were delineated on individual 4DCT phases, to define internal target volume (ITV). In particular, we delineated the ITV using the maximum intensity projection and verified the defined volume encompass of the tumor in each respiratory phase. Clinical target volume (CTV) was defined as equal to the GTV plus node-positive and hilar stations, and planning target volume (PTV) was created equal to the CTV and ITV, with a 0.5 cm safety margin. Whole lung and ipsilateral lung, excluding PTV, heart, oesophagus and spinal cord, were contoured as organs at risk (OARs).

Radiotherapy planning CT scans were accurately co-registered with SPECT scans. Iplan RT Image (v 4.1.2) was used to fuse CT simulation with SPECT, using an algorithm extracted using the Pyramid Approach to Sub-Pixel Image fusion based on mutual information (Brainlab Iplan RT image 4.1.2). For each patient LP, MP and HP were segmented based on SPECT intensity. Each perfusion area was adjusted to match the SPECT image size within the defined lung volume on planning CT (Fig. 1).

2.3.2 Treatment planning

Two different 3D-conformal plans were generated in a photon regimen with 6 MV nominal energies. The first plan was created without lung function information (Anatomic Plan, AP), while in the functional plan (FP) dose distribution was optimized according to low, medium and high perfusion contouring. Each plan was performed with a Varian Eclipse Treatment Plan System and calculated using the anisotropic analytical algorithm (version 10.0.28, varian medical systems, Palo Alto, CA, USA) (Fig. 2).

The total prescribed neoadjuvant dose (50.4 Gy; 5 day/week) was delivered in 28 fractions, with 95% of the PTV to be covered by 95% to 105% isodoses. Dose constraints for organs at risk are specified in Table 1 (modified from RTOG 0617) [6]. For each anatomical plan, the objective was to minimize the ipsilateral and whole lung volume receiving $\geq$20 Gy and the lung mean dose, without worsening the PTV coverage and respecting the OARs recommended constraints. For the functional plan, the primary objective was to minimize high perfusion (HP) and medium perfusion (MP) lung dose, while optimizing the HP and MP V_{20Gy}. Dose-volume histograms (DVHs) were

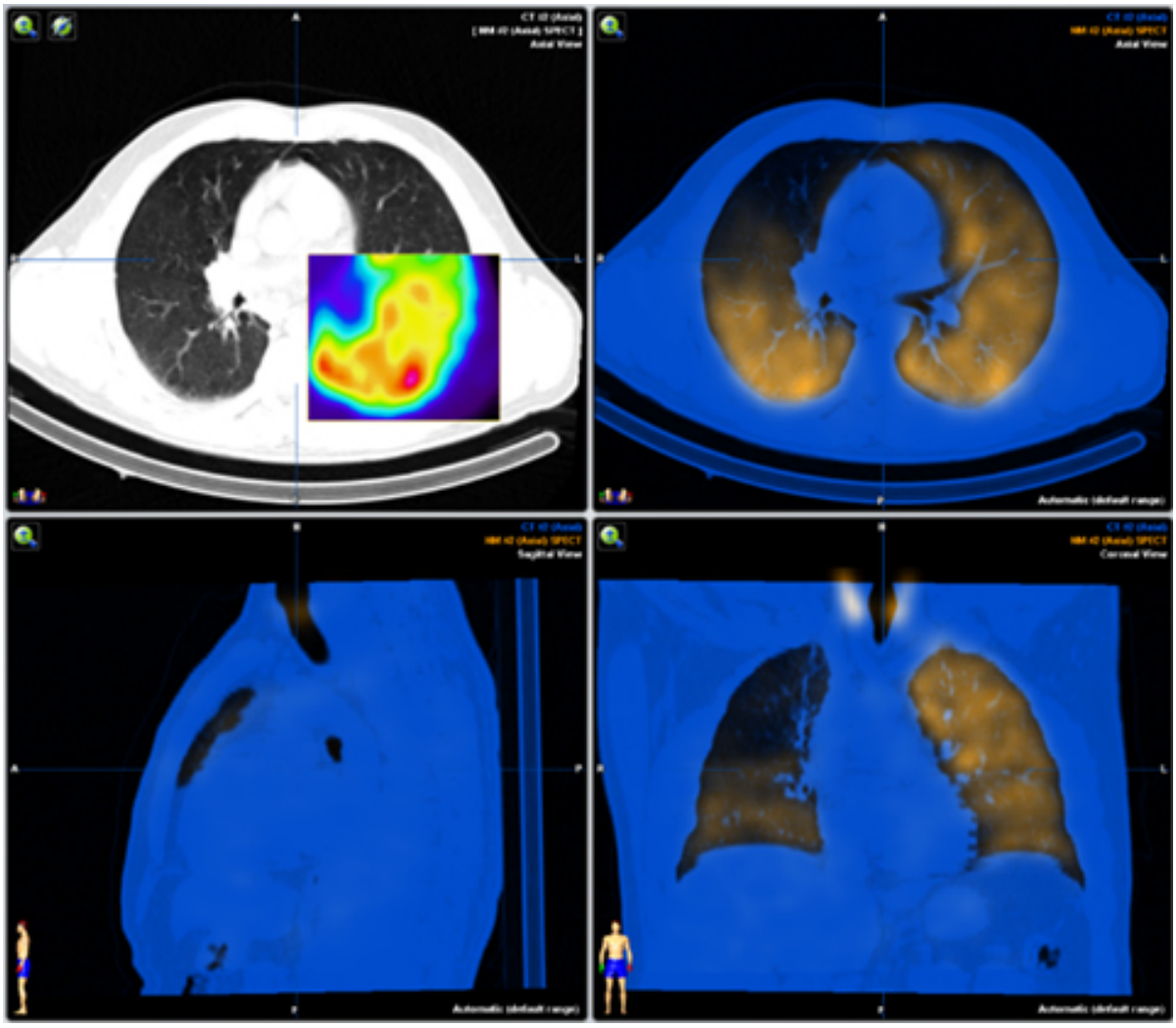

Fig. 1. Radiotherapy planning computed tomography (CT) scans co-registered with SPECT scans.

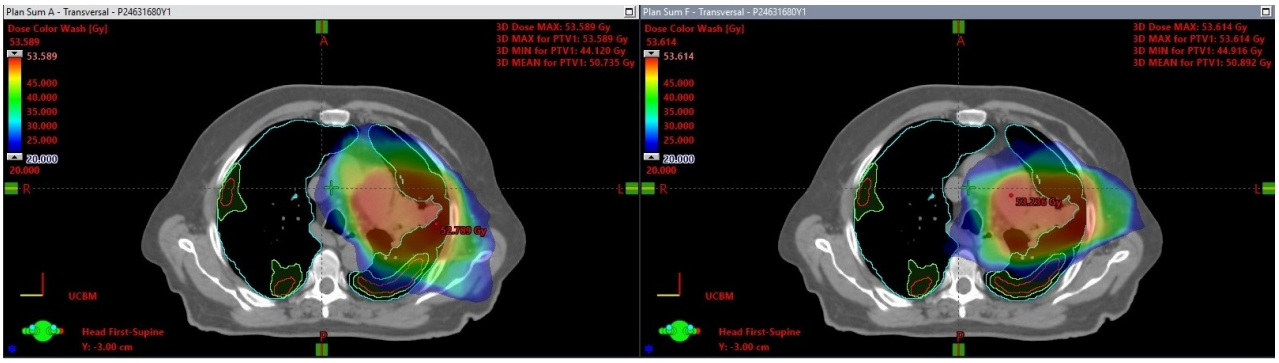

Fig. 2. Comparison of the dose distribution in anatomical plan (left) and in functional plan (right). Three different perfusion areas, based on SPECT intensity, were segmented: low perfusion (blue), medium perfusion (yellow) and high perfusion (red).

used to evaluate the dose to the target and to the organs at risk (OARs).

Several data was collected for whole lung-PTV and for each functional area, in both anatomic and functional plans (AP and FP). The dosimetric parameters for comparison between AP and FP were lung mean dose (lung D_{mean}), $WLV_{5-20-30Gy}$ (the percentage of whole lung-PTV volume receiving 5, 20 or 30 Gy) and ipsi$WLV_{20-30Gy}$ (the percentage of ipsilateral whole lung volume receiving 20 or 30 Gy). According to SPECT imaging, V_{5Gy}, V_{20Gy}, V_{30Gy} were computed for each functional area: HP, MP and LP.

Table 1. Dose constraints for organs at risk.

Structure	Description	Metric	Constraint
Heart	Heart/pericardium	Max dose (0.03 cc)	<70 Gy
		Mean dose	<30 Gy
		V30 Gy	<50%
		V40 Gy	<35%
Esophagus	Esophagus	Max dose (0.03 cc)	<74 Gy
		Mean dose	<34 Gy
Lungs	Bilateral lungs-PTV	Mean Dose	<20 Gy
		V20 Gy	<35%
		V5 Gy	<60%
	Ipsilateral lung-PTV	V20 Gy	<52%
Spinal cord		Max dose	45 Gy

Table 2. Patients' clinical characteristics.

Patient characteristics		N
Gender	Male	5
	Female	4
Age (y)	Median	71
	Range	58–81
Histologic type	Adenocarcinoma	5
	Squamous cell carcinoma	4
Stage	IIIA	8
	IIIB	1
Tumor location (patient number)	Upper lobes	5
	Lower lobes	3
	Hilar areas	1

To estimate the difference between dose coverage, three variables were reported: minimum dose at PTV (D_{min}), conformity index (CI) (defined as the ratio between the volume covered by the reference ICRU isodose of 95%, and the planning target volume (PTV)), and the homogeneity index (HI) (calculated as the ratio between the maximum dose in the PTV and the prescription dose [20,21]). Comparisons between the two planning techniques, taking into account doses to PTV and OARs, were performed by a non-parametric mann withney test. Statistical analysis was performed with SPSS version 24 (IBM Corp., Armonk, NY, USA) and the differences were considered statistically significant at $p \leq 0.05$ with a two-tailed test result.

3. Results

9 patients were planned and a total of 18 plans were available for analysis. Patients' clinical characteristics are summarized in Table 2. The median PTV was 156 cc (range: 88.8 cc–253.5 cc), and the median volume of whole lung was 3767 cc (range: 1810–5832 cc). Table 3 shows PTV values: total lung minus PTV and functional areas HP, MP and LP (%). There is a high variability between patients' functional area volumes (Fig. 3), with the median values being: HP 19.8% (1.7%–48,5%), MP 21% (4.4%–46%) and LP 59.1% (30,8%–85.2%) of the total lung.

Table 3. Patients' PTV and whole lung-PTV (WL-PTV) volume and percentage of the three different functional areas: high perfusion (HP), medium perfusion (MP), low perfusion (LP).

	PTV (cc)	WL-PTV (cc)	% HP	% MP	% LP
1	253.5	5260.0	6.0	9.0	85.1
2	173.2	2533.9	10.5	46.1	43.4
3	175.3	3439.4	17.2	24.1	58.7
4	224.7	1810.6	17.2	24.4	58.4
5	110.9	3331.6	48.5	20.7	30.8
6	123.0	3662.0	44.3	22.2	33.5
7	88.8	5832.0	2.5	25.4	72.1
8	90.5	4013.7	1.7	13.1	85.2
9	164.4	4018.0	30.8	4.4	64.8

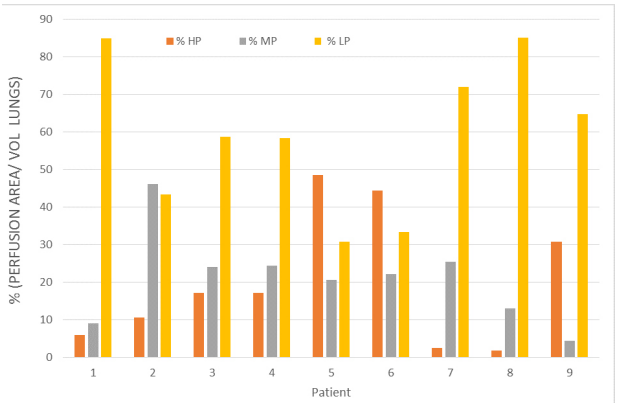

Fig. 3. Functional areas volumes for each patient (high perfusion (HP), medium perfusion (MP) and low perfusion areas).

No significant differences were found in PTV parameters between anatomical and functional plans resulting in a comparable PTV coverage: ${}^{A,F}D_{min}$(mean values are ${}^{A}D_{min}$= 44.46 Gy ± 2.3. ${}^{F}D_{min}$ 42.74 Gy ± 3.43 p = 0.332; ^{A,F}CI (^{A}CI 0.56 ± 0.13; ^{F}CI 0.52 ± 0.13 p = 0.367); e ^{A,F}HI (^{A}HI 1.06 ± 0.016; ^{F}HI =1.05 ± 0.014 p = 0.328).

In the functional plans, a significant reduction of dose in high perfusion areas was reported. The reduction of HP-V_{20Gy} values ranged from 15% to 8% (p = 0,046), the ipsiHP-V_{20Gy} from 38% to 22% (p = 0.028) and ipsiHP-D_{mean} reduction from 16 Gy to 12 Gy (p = 0.039).

For all plans (both anatomical and functional) the OARs constraints were met. No significant differences in the OARs metrics were reported between the two plans (see Table 4).

4. Discussion

In this dosimetric trial, the advantage of using SPECT lung functional information to optimize 3D treatment planning has been reported. With functional planning, reduction by half of V20 in the high perfusion areas has been obtained. Most studies which also evaluate the normal tissue-saving effect of modern radiation therapy techniques, consider to-

Table 4. Differences in the OARs metrics in anatomical and functional plan.

Heart	Dose contraints	Anatomical plan	Functional plan	*p* value
	Mean dose (Gy)	6.42	5.65	0.290
	V38	5.37	4.13	0.145
	V40	4.19	3.06	0.169
	V42	3.04	2.37	0.112
	V45	2.19	2.13	0.844
Oesophagus	Mean dose (Gy)	11.91	12.10	0.776
	V35	15.45	14.99	0.710
	V50	4.99	2.32	0.114
Spinal cord	Maximum dose	18.8	22.37	0.232
Lung	Mean dose (Gy)	13.25	13.17	0.32
	V20	10.78	11.49	0.25
	HP-V_{20Gy}	15	8	0.046
	ipsiHP-V_{20Gy}	38	22	0.028
	ipsiHP-D_{mean} (Gy)	16	12	0.039

tal lung as a uniform functional organ [11]. The SPECT or other functional imaging can, however, also provide spatial information on the lung's subunits activity. Subsequently, dose distribution for each radiotherapy treatment plan can be optimized according to the contribution of each area to pulmonary function, resulting in a reduced risk of lung damage. Radiation pneumonitis is one of the most common dose-limiting adverse effects of thoracic radiation treatment, and it can be life-threatening and significantly affect quality of life. The tumor and pre-existing lung comorbidities, such as chronic disease or smoking related alterations, may cause regional changes in lung perfusion.

SPECT provides information on the distribution of blood flow, as well as on the perfused areas that could coincide with the functional sites [22,23]. A recent systematic review and meta-analysis of the role of functional lung imaging reports showed improved Mean Lung Dose and V20 when plans were optimized to spare the functional lung, reporting that V20 was reduced by 4.2% (95% CI: 2.3–6.0) and MLD by 2.2 Gy (95% CI: 1.2–3.3) [13].

Function-guided IMRT planning seems to be more effective in preserving the functional lung area. As expected, IMRT compared to 3D-CRT allow us to reduce more effectively doses to functional lung defined by perfusion SPECT scan [15–17], incorporating perfusion information in IMRT planning.

Regarding the above, the median reductions in the mean lung doses in the functional plan compared with those in the anatomic plans can be relevant [16]. In Shioyama *et al*. [24], SPECT-CT was registered with simulation CT and was used to segment the 50- and 90-percentile hyperperfusion lung (F50 lung and F90 lung), with the median reductions in the mean doses to the F50 and F90 lung in the functional plan being 2.2 Gy and 4.2 Gy, respectively. Contrary to IMRT, the impact of integrating SPECT information in an optimized 3D conformal radiation therapy planning is not yet clear [24].

In literature, the feasibility of perfusion-weighted optimization was demonstrated in a virtual phantom consisting of three concentric cylinders, with different unit density material representing lung tumor, lung tissue and patient's body contour [25].

In our dosimetric study on real case patients, the SPECT-based 3DCRT led to a reduction of high perfusion areas treated with 20 Gy of about 50%. Moreover, functional plans did not increase doses to other OARs, such as esophagus and heart. Only the dose to the spinal cord was slightly increased in our series, yet remained very low (median value = 22.37 Gy). No class solution was used, but each plan was optimized and personalized taking into account the tumour volume and morphology, as well as the distribution of the functional areas of patients. We further demonstrated that with 3D conformal radiation therapy using functional imaging, very conformed plans can also be obtained without compromising target coverage or worsening dose distribution to the OARs.

The retrospective nature of the analysis, the limited number of cases reported, and bias caused by variability in patient characteristics and risk factors, are the main limitations of this study although results are very encouraging in this field and represent possibilities for further research.

Many studies analyzed in the aforementioned meta-analysis [13] did not report the potential harmful effects on the other organs at risk (OARs) apart from the lungs, focusing only on the potential advantage on the pulmonary parenchyma. An analysis of the possible effects caused by modifying treatment plan dose distribution is essential to explore potential negative effects on PTV's coverage and OARs dose constraints resulting from optimization to functional lung parameters. In particular, esophagus and heart doses can result in increased costs for patients: earlier treatment interruptions, need for hospitalization, worse outcomes [26].

5. Conclusions

Despite the few cases reported, the strength of our study lies in the reported benefit of functional lung information in 3D conformal radiation planning, and the demonstration that this can be obtained without compromising target coverage or worsening dose distribution to the OARs.

Prospective randomized clinical trials, with clearly defined toxicity endpoints, will conclusively clarify the role of SPECT and functional imaging in reducing pulmonary toxicity in clinical practice.

Author contributions

Conceptualization—SR and VV. Methodology—SR and RMD. Validation—MF, CG and SR. Formal Analysis—MF, EI, CG and CDV. Investigation—CG, MF, GR, MZ. Data Curation—CG, GR, MZ, EI, CDV. Writing—Original Draft Preparation—CG, MF and VV. Writing—Review & Editing—CG, MF and SR. Supervision—AG and SR. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

Data sharing statement

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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