Radiotherapy and Oncology 172 (2022) 118–125

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic Review

Exposure of the heart in lung cancer radiation therapy: A systematic review of heart doses published during 2013 to 2020

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ARTICLE INFO

Article history:
Received 17 January 2022
Received in revised form 26 April 2022
Accepted 8 May 2022
Available online 13 May 2022

Keywords:
Lung cancer
Cardiac exposure
Radiotherapy strategies

ABSTRACT

Background and purpose: Lung cancer radiotherapy increases the risk of cardiotoxicity and heart radiation dose is an independent predictor of poor survival. This study describes heart doses and strategies aiming to reduce exposure.

Materials and methods: A systematic review of lung cancer dosimetry studies reporting heart doses published 2013–2020 was undertaken. Doses were compared according to laterality, region irradiated, treatment modality (stereotactic ablative body radiotherapy (SABR) and non-SABR), planning technique, and respiratory motion management.

Results: For 392 non-SABR regimens in 105 studies, the average MHD was 10.3 Gy (0.0–48.4) and was not significantly different between left and right-sided tumours. It was similar between IMRT and 3DCRT (10.9 Gy versus 10.6 Gy) and lower with particle beam therapy (proton 7.0 Gy; carbon-ion 1.9 Gy). Active respiratory motion management reduced exposure (7.4 Gy versus 9.3 Gy). For 168 SABR regimens in 35 studies, MHD was 4.0 Gy (0.0–32.4). Exposure was higher in central and lower lobe lesions (6.3 and 5.8 Gy respectively). MHD was lowest for carbon ions (0.5 Gy) compared to other techniques. Active respiratory motion management reduced exposure (2.4 Gy versus 5.0 Gy). Delineation guidelines and Dose Volume Constraints for the heart varied substantially.

Conclusions: There is scope to reduce heart radiation dose in lung cancer radiotherapy. Consensus on planning objectives, contouring and DVCs for the heart may lead to reduced heart doses in the future. For IMRT, more stringent optimisation objectives may reduce heart dose. Active respiratory motion management or particle therapy may be considered in situations where cardiac dose is high.

Lung cancer is the most common cancer worldwide with an incidence of 2.2 million reported in 2020 [1]. Radical radiotherapy (RT) is used to treat locally advanced non-small cell lung cancer (NSCLC), early-stage NSCLC not suitable for surgery, and limited stage small cell lung cancer (SCLC). Incidental exposure of the heart is unavoidable in most patients, and this may increase the risk of cardiac disease including ischaemic heart disease, heart failure, valvular heart disease, pericardial disease, and conduction system abnormalities [2,3]. Injury to the heart can manifest clinically many years after RT [4] but acute cardiotoxicity may also occur within a few months post treatment, particularly in patients with lung cancer [5,6]. The association between cardiac radiation exposures and subsequent cardiotoxicity is well established for patients undergoing RT for breast cancer [7,8] and Hodgkin's lymphoma [9–11] and cardiac-sparing techniques are routinely incorporated into treatment planning and delivery [12,13]. Given the poor prognosis traditionally associated with lung cancer, most toxicity studies have focused on acute radiation-related pneumonitis [14–16] and oesophagitis [17–19]. However, cardiac toxicity is a real concern for this group of patients. Lung cancer survival is improving due to early detection, tobacco control interventions and improved treatments. The cohort of patients involved are typically greater than 60 years and may have a history of cardiac disease or pre-existing factors for developing cardiac disease e.g., smoking, hypertension [20,21]. There is increasing evidence available on the risk

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https://doi.org/10.1016/j.radonc.2022.05.007
0167-8140/

of cardiac morbidity and mortality relating to radiation dose delivered to the heart and there is a need to develop dose–response relationships for radiation-related heart disease in this population.

The RTOG 0617 randomised trial reported an association between heart dose parameters (such as heart V5) and poorer overall survival [22,23]. Two lung cancer studies reported a relationship between MHD and coronary events. In one study of patients with no pre-existing cardiac disease a MHD > 10 Gy predicted major coronary events [24]. In another study of patients with pre-existing cardiac disease MHDs of 5 and 12 Gy predicted grade $\geq$ 3 cardiac event rates of 10% and 15% respectively [21].

The aim of this study is to present a systematic review of heart doses reported in in the modern era of lung cancer RT, including heart dose variation according to region irradiated, laterality, treatment modality and planning technique. It aims to summarise treatment strategies, such as motion management or use of particle therapies, which may lead to a reduction in heart dose. This work may guide the design of epidemiological and clinical studies investigating radiation-related heart toxicity in patients with lung cancer.

Materials and methods

Study identification

EMBASE and SCOPUS electronic databases were searched for publications using the following terms in the title or abstract: 'dos* AND lung* AND cancer/carcinoma/tumor/tumour/ AND radiation/radiotherap' to retrieve all lung cancer studies reporting radiation dosimetry information published between January 1st 2013 and October 10th 2020.

Study eligibility criteria

Eligible studies were identified using the Preferred Reporting Items for Systematic Reviews guidelines (Fig. 1) [25]. Studies reporting heart exposure from diagnostic imaging or from occupational/environmental radiation exposure and studies of lung cancer metastases located outside the thorax or of thoracic tumours that were not lung cancer e.g., thymoma and mesothelioma were excluded. Reviews, case studies and surveys were also excluded. All studies reporting any measure of whole heart or doses to cardiac substructures, the pericardium or the great vessels were eligible for inclusion in the study, and the treatment parameters associated with each heart dose reported within a study was described as a "regimen". In total 1031 RT regimens in 281eligible studies were identified (Fig. 1, Table 1, Table S6).

Data extraction

For each eligible study the following variables were extracted for each regimen reported: author, year, country of first author, RT dose fractionation schedule, treatment modality, radiation modality, histology, location of primary tumour (laterality and lobar location), treatment planning technique, type of respiratory motion management used, cardiac delineation details, treatment

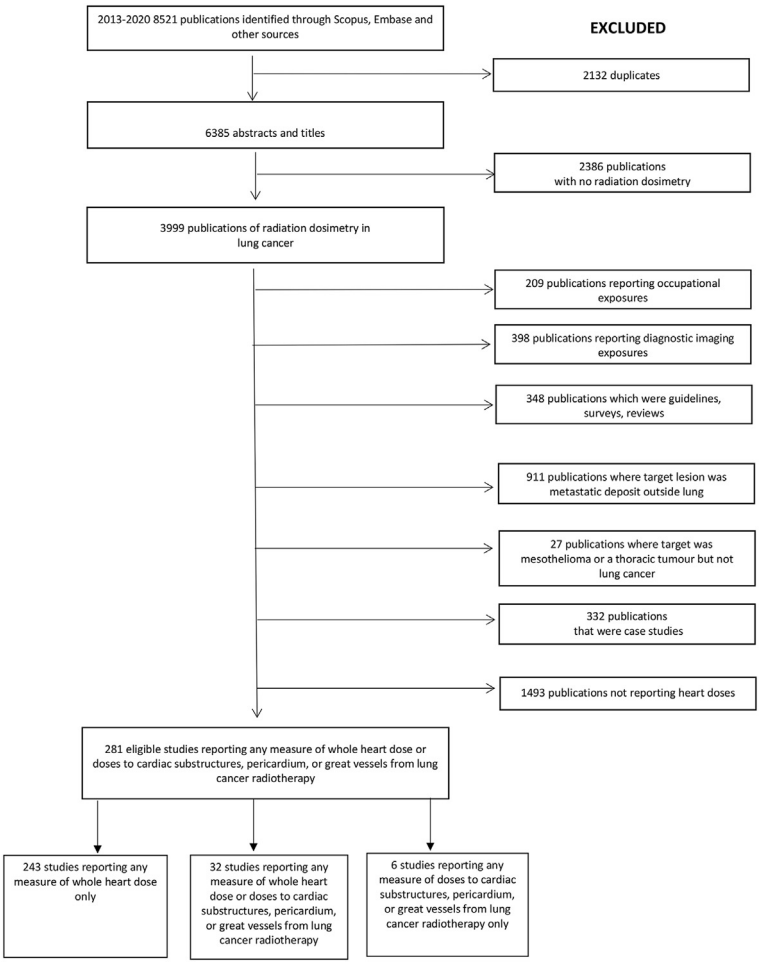

Fig. 1. The process of study identification for the review.

planning algorithm used, number of CT plans per regimen included in the study and whether the treatment plan was delivered (Table S1, S6, Text S1). The tumour locations recorded included the lobar location of the lesion and whether the lesion was central, ultracentral or peripheral (Table S1). Regimens were categorised according to (1) treatment modality: stereotactic ablative body radiotherapy (SABR) or non-SABR RT (conventional or hypofractionated dose schedules, 1.5–3 Gy), (2) radiation modality: photon beam therapy or particle beam therapy (3) treatment planning technique: 3D-conformal RT; intensity modulated RT (static gantry IMRT, volumetric modulated arc therapy, helical tomotherapy, dynamic conformal arc therapy, MR-Linac); robotic driven delivery systems (cyberknife or X-knife); or particle beam therapy (protons or carbon ions) and (4) respiratory motion management: no respiratory motion management; non-active (Internal Target Volume approach, MidVentilation, MidPosition); or active (inspiration breath hold, expiration gating, inspiration gating, abdominal compression, respiratory tracking) (Table S1, Fig. 2). Dose optimiser objectives (the dose goal for the various structures and the priority of meeting each goal during the plan optimisation process) and dose volume constraints (DVCs) for the heart were extracted for IMRT and particle beam therapy regimens only. This was to determine the priority of the heart in inverse planning optimisation. For a thorough description of dose calculation algorithms reported in

Table 1
Studies reporting cardiac doses from lung cancer radiotherapy regimens published 2013–2020.

Dose Measure	Treatment Modality	Histology	Tumour Stage	Tumour Location	Number of Studies[1]	Number of RT regimes[2]	CT plans per regimen		Heart Dose (Gy)	
							Average	Range	Average	Range
Mean Whole Heart Dose	**SABR**			**Total**	**35**	**168**	13	1–189	**4.0**	0.0–32.4
		All	All	RLL	2	8	1	1–1	4.2	1.6–9.0
		All	All	RML	2	4	1	1–1	4.0	2.4–5.3
		All	All	RUL	3	13	1	1–1	3.0	0.1–17.6
		All	All	Central[3]	5	20	20	1–109	6.3	0.3–19.3
		All	All	LUL	5	25	1	1–1	1.8	0.1–16.1
		All	All	LLL	2	17	1	1–1	5.8	0.7–32.4
		All	All	Not specified	29	81	23	1–189	4.0	0.0–23.0
Mean Whole Heart Dose	**non-SABR[4,5]**			**Total**	**105**	**392**	**32**	**1–748**	**10.3**	**0.0–48.4**
		NSCLC	Stage I	All	2	2	22	13–31	2.7	1.9–3.6
		NSCLC	Stage II	All	1	2	1	1–1	12.4	5.9–19
		NSCLC	Stage III	All	28	92	45	1–746	12.4	0.0–32.4
		NSCLC	Stage IV	All	1	5	1	1–1	14.1	4.1–22.0
		SCLC	Limited Stage	All	3	6	45	10–80	16.4	13.7–18.6
		All	Not specified	All	72	285	27	1–748	9.4	0.0–48.4
	All studies reporting mean heart dose				**140**	**560**	**29**	**1–748**	**8.4**	**0.0–48.4**
Maximum Whole Heart Dose	**SABR**			**Total**	**49**	**194**	**22**	**1–189**	**20.8**	**0.0–84.0**
		All	All	RLL	2	6	9	1–25	17.6	0.8–44.0
		All	All	RML	2	5	3	1–5	47.5	20.4–65.3
		All	All	RUL	4	12	2	1–5	20.1	1.2–51.1
		All	All	Central[3]	4	23	3	1.35	29.9	1.1–63.0
		All	All	LUL	2	9	1	1–1	13.4	3.2–30.6
		All	All	LLL	2	14	2	1–5	23.4	9.5–54.7
		All	All	Not specified	39	125	19	1–189	19.4	0.1–84.0
Maximum Whole Heart Dose	**non-SABR[4,5]**			**Total**	**23**	**77**	**16**	**1–83**	**44.1**	**0.3–86.4**
		NSCLC	Stage I	All	1	1	13	13–13	35.1	35.1–35.1
		NSCLC	Stage II	All	0	0	na	na	na	na
		NSCLC	Stage III	All	3	11	13	3–26	41.7	0.3–71.0
		NSCLC	Stage IV	All	0	0	na	na	na	na
		SCLC	Limited Stage	All	1	2	10	10–10	62.9	61.5–64.3
		All	Not specified	All	18	63	29	1–748	44.0	4.2–86.4
All studies reporting max whole heart dose					**73**	**271**	**14**	**1–189**	**27.4**	**0.1–86.4**
All SABR studies reporting some measure of whole heart dose					**98**	**391**				
All non-SABR studies reporting some measure of whole heart dose					**177**	**587**				
All studies reporting some measure of whole heart dose					**275**	**978**				
All studies reporting some measure of substructure dose[6]					**38**	**130**				
All Studies [7]					**281**	**1003**				

Definitions: SABR: Stereotactic ablative radiotherapy, RLL: Right Lower lobe, RML: Right Middle Lobe, RLL: Right Lower lobe, LUL: Left Upper Lobe, LLL: Left Lower Lobe, NSCLC: Non Small Cell Lung Cancer, SCLC: Small Cell Lung Cancer, MHD: Mean Heart Dose, Max Heart dose: Maximum Heart dose.
All doses reported refer to physical dose.

[1] Some studies contributed doses for several regimens and so contribute more than once.

[2] Some regimens reported several dose measures e.g MHD and max heart dose.

[3] Includes one regimen that was categorised as ultracentral, Four studies did not specify how central tumours were defined, two studies referred to RTOG 0236 guidelines i.e. within 2 cm of the proximal bronchial tree and one study referred to RTOG 0813 guidelines i.e. tumors within or touching the zone of the PBT, defined as a volume of 2 cm in all directions around the PBT, a tumor within 2 cm in all directions around the PBT and immediately adjacent to mediastinal or pericardial pleura (PTV touching the mediastinal pleura).

[4] Includes all non-SABR regimens reporting a conventional or hypofractionated dose schedule. Dose per fraction of 1.5–3.0 Gy per fraction was reported in non-SABR regimens.

[5] Non-SABR regimens were reported by tumour stage rather than location as mean heart dose and maximum heart dose was reported by lobar location in just 16%(64/392) regimens in (19/105) studies while information on tumour stage was available for 27%(107/392) regimens in34/105 studies.

[6] This total represents 32 studies and 105 regimens also reporting whole heart doses and 6 studies and 25 regimens reporting substructure dose only.

[7] This total represents the number of studies reporting some measure of whole heart and substructure dose.

studies please refer to Martino et al. [26]. Physical doses for the whole heart and doses to cardiac substructures, the pericardium and the great vessels were extracted from all regimens including volumetric and point doses. Doses reported relate to physical dose rather than the biologically effective dose to the heart as physical doses were reported and dose volume histograms were not available to allow conversion to EQD2.

Data analyses

Meta-analyses considered the average whole heart dose measures from the CT plans included for each regimen described in each study. Whole heart doses (average mean heart dose and average maximum heart dose) were compared according to laterality, lobar regions irradiated, treatment modality, radiation modality, treatment planning technique, and use of respiratory motion management techniques. Findings were reported separately for SABR and non-SABR regimens as the rationale for both techniques vary. Average mean heart dose and its 95% confidence interval was plotted along reported ranges. Under the fixed-effect model, the heterogeneities between and within SABR and non SABR regimens were tested by the method of variance-weighted least squares (VWLS). VWLS treats the estimated variance as if it were the true variance therefore it takes account different study sizes into heterogeneity test.

Results

In total, 978 regimens in 275 eligible studies were identified (Table 1, Table S6, Text S1-S2). 391 regimens in 98 studies were SABR studies and 587 regimens in 177 studies were non-SABR studies. Mean heart dose was the dose-parameter most reported in 560/978 (57%) regimens in 140/275 (51%) studies. This was followed by maximum heart dose reported in 271/978 (28%) regimens in 73/275 (26%) studies. Other dose measures were reported less frequently e.g., V5 (the volume of heart (%) receiving 5 Gy) reported in 88/978 (9%) of regimens in 28/275 (10%) studies, V30 reported in 167/978 (17%) regimens in 56/275 (20%) studies and V60 reported in 56/978 (6%) regimens in 20/275 (7%) studies

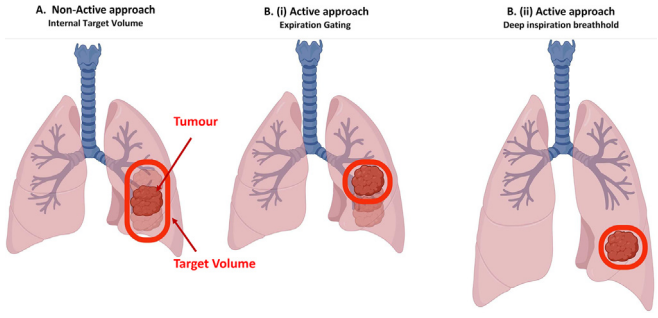

Fig. 2. Respiratory motion management in lung cancer radiotherapy. Illustration of the most common approaches to respiratory motion management in lung cancer. (A) Non-active respiratory motion management, often referred to as "motion-encompassing". A 4-D CT or respiration-correlated CT acquires images in a number of respiratory phases. An ITV (internal target volume) is delineated which encompasses the tumour in all respiratory phases. Alternative approaches (closely related) include the mid ventilation approach and the mid-position approach (not illustrated), which involve planning on the time-weighted average position of the tumour using 4-D CT data. (B) Active respiratory motion management reduces the impact of respiratory motion in radiotherapy using (i) gating (delivery treatment during a particular phase of the breathing cycle referred to as the 'gate') (ii) breathing control e.g. deep inspiration breath-hold. Other techniques include abdominal compression inducing shallow breathing and real time tumour tracking (not illustrated). Created using BioRender.

(Table S6). The MHD reported for all regimens combined was 8.4 Gy (0.0–48.4) (Table 1, Fig. 3). For SABR, MHD was reported for 168/391 (43%) regimens in 35/98 (36%) studies. The average MHD was 4.0 Gy (0–32.4). For non-SABR, MHD was reported for 392/587 (66.6%) regimens in 105/179 (59%) studies. The average MHD was 10.3 Gy (0–48.4).

Heart doses varied according to location and disease stage (Table 1). For SABR, MHD was higher in right-sided regimens (4.6 vs. 2.9 Gy) (Table S2). Information on lobar location of the primary lung lesion was available for 87/168 (54%) SABR regimens reporting mean heart dose, which was highest for central and left lower lobe lesions (6.3 Gy and 5.8 Gy respectively), and lowest for right and left upper lobe lesions (3.0 Gy and 1.8 Gy respectively). The highest maximum heart doses were for right middle lobe (47.5 Gy) and central (29.9 Gy) lesions – over 4 times the maximum heart dose reported for left upper lobe lesions (13.4 Gy). For non-SABR, information on tumour location was lacking. MHD was reported by lobar location in just 64/392 (16%) regimens in 19/105(18%) studies and by laterality in just 61/391(16%) of regimens in 14/105 (13%) studies. Exposure was not significantly different between left and right-sided tumours (Table S2). For non SABR studies MHD was reported by tumour stage for 107/392 (27%) regimens in 34/105 (32%) studies reporting MHD. 92/107 regimens in 28/34 studies included Stage III NSCLC while the remainder targeted Stage I (2/107), Stage II (2/107), Stage IV (5/107)and limited stage SCLC (6/107). Average mean heart dose was 12.4 Gy (0–32.4) for Stage III disease (Table 1).

Heart doses varied according to radiation modality and treatment planning technique used (Fig. 3). For SABR regimens, 162/168 (96%) were delivered using photon beam therapy and 6/168 (4%) using particle beam therapy. MHDs were lower for particle beam therapy regimens (2.0 Gy vs. 4.1 Gy). There was no statistical difference between MHDs from various photon-planning techniques. Average mean heart doses were similar for 3DCRT (3.3 Gy (0.3–10.3)) and IMRT (4.6 Gy (0–32.4)), $p = 1.0$. For SABR studies, dose optimiser objectives were described for one study [27] while heart DVCs were described in only 25% (11/45) of IMRT studies and 38% (3/8) of particle beam therapy studies reporting mean heart dose and/or maximum heart dose (Table S3). Five studies referred to RT guidelines or protocols and nine studies described specific DVCs. The most common DVCs reported were maximum heart dose < 30 Gy and the volume of the heart receiving 46 Gy < 0.03 cc, each reported in two studies (Table S4). For non-SABR regimens 343/392 (87%) were delivered using photon beam therapy and 49/392 (13%) using particle beam therapy (Fig. 3). For photons average MHDs were similar between 3DCRT and IMRT 10.6 Gy (0–24.5) and 10.9 Gy (0–48.4) respectively. MHDs were lower for particle beam therapy (6.9 Gy). Optimiser dose objectives were described in 2 studies [28,29] while heart DVCs were described in only 37% (23/62) of IMRT studies and 21% (3/14) of particle therapy studies reporting mean and/or maximum heart dose (Table 2). Three studies referred to guidelines or protocols and the remaining 23 studies described specific DVCs. Mean heart dose < 26 Gy was the common DVC reported in 4 studies.

Heart doses varied according to respiratory motion management (Fig. 4). For SABR, 136/168 regimens in 18/35 studies reported mean heart doses where respiratory motion management techniques were used. Active motion management techniques were reported in 83/136 (61%), non-active motion management techniques in 48/136 (35%) and no motion management was used in 5/136 (4%) of regimens. Mean heart doses reported using active motion management techniques were half those reported using non-active motion management strategies (2.4 vs. 5 Gy). Lowest mean heart doses were reported when inspiration breath hold was used (2 Gy (0.1–5.1)). For non-SABR 208/392 (54%) regimens

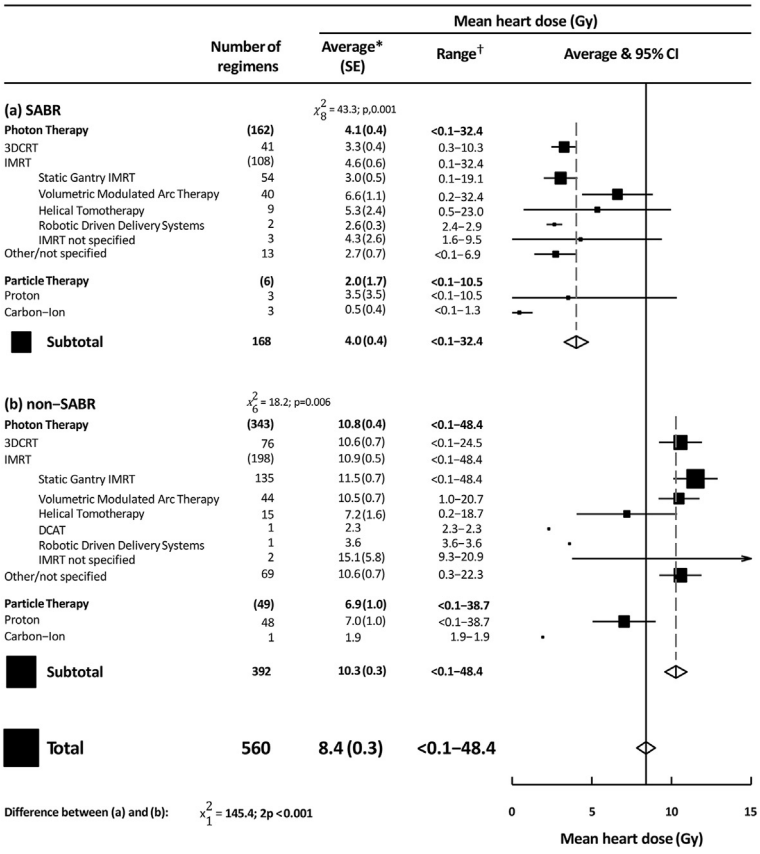

Fig. 3. Average whole mean heart doses reported in lung cancer radiotherapy published 2013–2020 according to radiotherapy treatment modality, radiation modality and treatment planning technique used. Radiotherapy planning technique definitions are provided in Table S1. Abbreviations: Gy: gray; SE: standard error; CI: confidence interval; SABR: stereotactic ablative body radiotherapy; IMRT: intensity modulated radiotherapy; DCAT: dynamic conformal arc therapy. *Average of mean heart doses for reported regimens. †Range of mean heart doses for reported regimens. χ^2_1 for linear trend test, χ^2_n for heterogeneity test. All doses reported refer to physical doses.

in 63/105 (60%) studies reported mean heart doses where respiratory motion management techniques were used. Non-active motion management techniques were reported in 168/208 (81%), active motion management techniques in 19/208 (9%) and no motion management was used in 21/208(10%) regimens. Respiratory motion management use reduced exposure with MHD of 11.4 Gy, 9.3 Gy and 7.4 Gy reported for no motion management, non-active motion management and active motion management respectively.

Various contouring guidelines for the heart, cardiac substructures, pericardium, and great vessels were specified in 39/285 (13%) studies (Table S4). 19 studies referred to international protocols, 10 referred to published atlases while 10 gave anatomical landmarks for delineation (S4). 38 studies and 130 regimens reporting doses to cardiac substructures, the pericardium or the great vessels were identified (Table S5, Text S2) with heterogeneity in the range of structures and corresponding dose metrics reported. For SABR studies, D0.1 cc Aorta (the minimum dose received by 0.1 cc of the aorta) was most commonly reported in 25/90 (27.8%) regimens in 1/28(3.6%) studies. For non-SABR studies, the doses received by 67% and 33% of the pericardium were most commonly reported in 18/49 (36.7%) regimens in 2/18 (11.1%) studies (Table S5).

Discussion

This systematic review of heart doses in lung cancer RT regimens published between 2013 and 2020 demonstrates the heterogeneity of heart doses in clinical practice and reports a number of strategies that influence cardiac exposure systematically. MHD was reported in over half the studies identified, suggesting that our results truly reflect average cardiac exposure during 2013–2020. It was not possible to extend our analyses beyond MHD as other parameters were reported less frequently. As yet there are no international guidelines on dose reporting for the heart or substructures of the heart specific to lung cancer RT. Quantec specified mean heart dose (MHD) < 26 Gy as a dose volume constraint (DVC) for thoracic RT but this constraint was not confirmed from RT studies in patients with lung cancer [30]. Dose distribution is not homogenous within the complex structure of the heart [31] and a number of recent studies have suggested specific dose parameters beyond MHD associated with cardiac events that may be considered in dose reporting. These include V30 < 50% (volume of the heart receiving 30 Gy should be < 50%), V45 < 35% [32], V5 should be as low as possible [23,33] left anterior descending coronary artery (LADCA) V15 > 10% and left ventricle V15 < 1% [24]. The percentage of studies reporting, whole heart V30 and V45 was 20% and 5% respectively. LADCA V15 and left ventricle V15 were not reported in any of the studies identified. This may be because these parameters were only specified in studies published as recently as 2018 and 2020. Our study also demonstrates that cardiac contouring guidelines and atlases used vary between studies which contributes to dose reporting uncertainties. An international consensus on the use of cardiac contouring atlases and dose reporting may be warranted to provide recommendations for the heart specific to lung cancer RT in clinical practice.

As expected, heart radiation doses (physical doses) were much less for SABR than non-SABR regimens (MHD 4.0 (range < 0.1–32.4)

Table 2
Dose Volume Constraints for the heart described in IMRT and particle beam therapy non-SABR regimens reporting mean and maximum heart dose in lung cancer radiotherapy 2013–2020.

Planning Technique	% (no.)dosimetry studies describing dose-volume constraints	Dose Volume Constraints	Study
IMRT	**37% (23/62)**		
		Referred reader to trial protocols/guidelines	
		RTOG 0618 and RTOG 0236	Troost et al, 2020
		RTOG 0617 for NSCLC, RTOG 0538 for SCLC	Vinogradskiy et al, 2018
		Dose Volume Constraint Specified	
		MHD < 26 Gy	Kapoor et al, 2020
		MHD < 26 Gy, Dmax: V25 Gy < 10%, V30 Gy < 46%, V50 Gy < 40%	Creemers et al, 2019
		MHD ≤ 26 Gy, V30Gy ≤ 40%, V40Gy ≤ 30%	Shao et al, 2019
		MHD < 32 Gy	Li et al, 2020
		MHD < 35 Gy	Kenamond et al, 2018
		MHD ≤ 30 Gy	Wu et al, 2018
		MHD < 35 Gy	Thomas et al, 2018
		MHD < 46 Gy, V50 < 20%	Ottosson et al, 2015
		MHD < 26 Gy, V30 < 40 Gy	Zhang et al, 2017
		MHD < 15 Gy	Gala et al, 2017
		Max dose ≤ 35 Gy, V40Gy ≤ 60%	Xu et al, 2017
		D1cc < 78 Gy	Hoffmann et al, 2017
		V20Gy < 20%	Bansal et al, 2019
		V25Gy < 50%, V40Gy ≤ 30%	Josipovic et al, 2018
		V30Gy ≤ 50%	Jaksic et al, 2018
		V30Gy ≤ 50%, V45Gy ≤ 35%	Jeter et al, 2018
		V40Gy ≤ 30%	Wong et al, 2020
		V40Gy < 66%, V50Gy < 66%,V66Gy < 33%	van-Diessen et al, 2019
		V45Gy < 66%	Waxweiler et al, 2017
		V45Gy < 67%, V65Gy < 33%	Zhao et al, 2020
		V60Gy < 33%	Temelli et al, 2020
Particle Therapy	**21% (3/14)**		
		Referred reader to trial protocols/guidelines	
		RTOG 0618 and RTOG 0236	Troost et al, 2020
		Dose Volume Constraint Specified	
		MHD < 20 Gy, V50[RBE] < 25%	Liu et al, 2019
		V30 ≤ 50%, V45 ≤ 35%	Jeter et al, 2018

Abbreviations: IMRT: Intensity Modulated Radiation Therapy; MHD: Mean Heart Dose; Max Dose: Maximum Heart dose; NS: not specified, RBE: Relative Biological Effectiveness.
Definitions VXXGy < XX% or xx cc: the volume of the heart receiving XX Gy must be less than XX% or xx cc.
D1cc < 78 Gy: Dose received by 1 cubic centimetre of the heart must be less than 78 Gy.

vs 10.3 Gy (range < 0.1–48.4)). For SABR, exposure was higher in central and lower lobe lesions (6.3 and 5.8 Gy respectively) compared to other locations. MHD was lowest for carbon ions (0.5 Gy) compared to other techniques. Active respiratory motion management reduced exposure (2.4 Gy versus 5.0 Gy). For non-SABR, MHDs were not significantly different between left and right-sided tumours. For non-SABR photon-based therapy MHDs were similar between IMRT and 3DCRT (10.9 Gy versus 10.6 Gy). The most common heart DVC used for inverse planned IMRT was MHD < 26 Gy. MHDs were lower with particle therapy (proton 7.0 Gy; carbon-ion 1.9 Gy) and active respiratory motion management significantly reduced exposure (7.4 Gy versus 9.3 Gy).

Despite clear evidence of excess cardiac exposure in left-sided breast cancer RT [34] this was not observed in left-sided lung cancer RT. This suggests that a reliable indication of the effect of RT on the heart may not be obtained by comparing outcomes for patients with left-sided lung tumours to those with right-sided tumours. Lobar location may be a more significant indicator of prognosis with lower lobe tumours associated with poor prognosis in NSCLC [35,36]. In lung cancer, there has been a shift from 3DCRT to IMRT planning techniques and the use of particle beam therapy. IMRT was most frequently reported planning technique in lung cancer RT in this study except in complex cases where IMRT in the presence of multiple or larger lesions failed to meet dose volume constraints [32,37,38]and particle therapy was used. Despite wide use of inverse planning our results show that heart doses are similar from 3DCRT and IMRT regimens. This result is in contradiction with that of RTOG0617 showing that IMRT reduces heart doses [39]. The most common heart DVC reported was MHD < 26 Gy suggesting there may be scope to tighten heart DVCs. It may be possible to further prioritise the heart in plan optimisation. Only two studies emphasise heart dose as a clinical priority and non-co planar arcs were used for avoidance [40,41]. Studies emphasised using partial arcs to reduce contralateral lung dose [42–44] and planning optimisation to specifically reduce pneumonitis [45,46] and secondary breast cancer risk [46]. Particle therapy, specifically C-Ion, reduced mean and maximum heart doses in early stage SABR patients [37]. Active respiratory motion management, most commonly deep inspiration breath hold, resulted in lower heart doses and was commonly reported in SABR regimens in our study. This may be due to the increased tumour motion observed in early-stage NSCLC compared with locally advanced disease where a non-active approach could lead to the irradiation of excess healthy tissue. Non-active respiratory motion management was commonly used in non-SABR regimens and resulted in cardiac sparing compared to studies where no motion management was used. Overall, for non-SABR, an active approach resulted in lower cardiac exposures with average mean heart doses using expiration gating half those reported using the internal target volume non-active approach. Average mean heart doses were not reduced with breath-hold techniques specifically but these regimens involved patients where elective nodal irradiation was delivered and avoidance of the oesophagus was prioritised during optimisation [47].

Our study has several strengths. This is the first systematic review of heart doses in lung cancer RT. Data was extracted by an oncologist and radiation therapist and checked by a physicist.

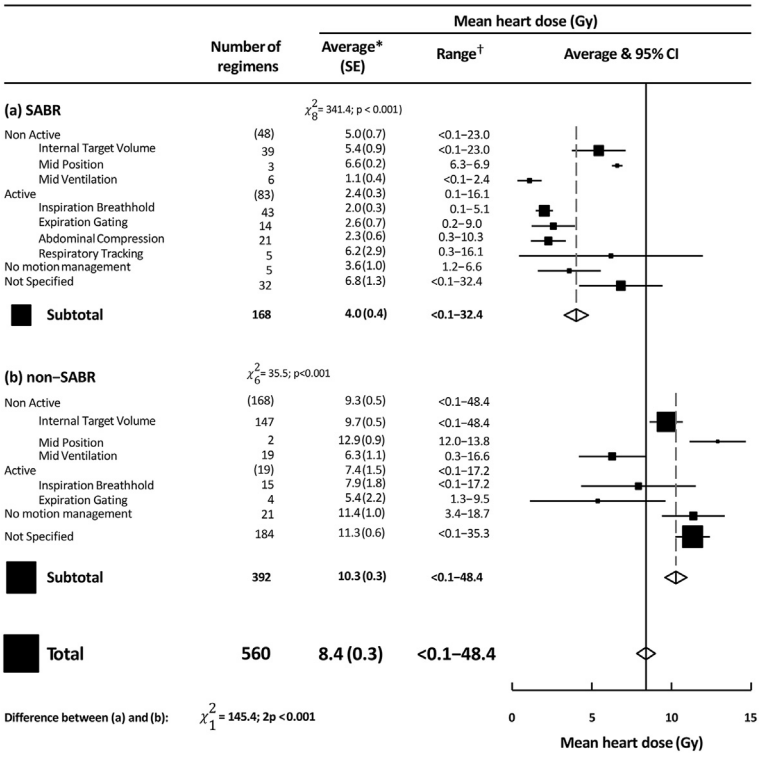

Fig. 4. Average whole mean heart doses reported in lung cancer radiotherapy published 2013–2020 according to respiratory motion management. Respiratory motion management technique definitions are provided in Fig. 2 and Table S1. Abbreviations: Gy: gray; SE: standard error; CI: confidence interval; SABR: stereotactic ablative body radiotherapy. *Average of mean heart doses for reported regimens. †Range of mean heart doses for reported regimens. χ^2_1 for linear trend test, χ^2_n for heterogeneity test. All doses reported refer to physical doses.

There was a wide search strategy capturing relevant studies. Our study has a number of limitations. Doses reported relate to physical dose only. This is due to the nature of the linear quadratic model where calculating the EQD2 of the mean dose of a whole organ would lead to an incorrect estimate of the effective dose, especially in the presence of sharp dose gradients present in SABR or proton plans. Information on PTV volumes sizes was not always reported and could not be systematically extracted so it was not possible to identify the impact tumour size has on treatment planning technique chosen and associated cardiac exposure. In addition, information on clinical outcomes was limited in the studies identified and it was not possible to summarise cardiac exposures and clinical cardiac events.

It is as yet unclear which regions of the heart are most sensitive to radiation induced injury and the dose thresholds to apply in the routine setting [48]. Pre-existing cardiac conditions may merit more stringent dose volume constraints [49] but inconsistency in reporting of cardiac endpoints and baseline cardiac risk mean that further validation is required [24]. The need to identify specific cardiac substructures and dose volume relationships to improve cardiac risk estimation is consistently cited [24]. More widespread reporting of cardiac dosimetry is essential, and this may be facilitated by developing international consensus guidelines around the topic to create awareness of what is needed to facilitate clinical research.

In conclusion, there is scope to reduce heart radiation doses in lung cancer RT. For photon based IMRT, the most common technique used in the clinic, more stringent planning optimisation objectives may reduce heart dose. Active respiratory motion management or particle therapy may also be considered where cardiac dose is high. There is an unmet need to understand the underlying mechanisms leading to RT-related cardiac toxicity and the impact on the sub-structures of the heart. Such information is vital in order to develop studies leading to the definition of more precise dose limits for the heart and substructures of the heart. In addition, consensus on planning objectives, contouring and DVCs for the heart are important objectives in order to validate more accurate dose volume relationships resulting in improved outcomes in patients with lung cancer.

Acknowledgements

M Keys received funding from HSE-NDTP Aspire Post-CSCST Fellowship Award, Ireland. ZW and MA received funding from Cancer Research UK grant C8225/A21133. Professor Faivre-Finn is supported by a grant from the NIHR Manchester Biomedical Research Centre. M Kearney and FD received no funding. Professor Faivre-Finn and MA received funding from Cancer Research UK RadNet Manchester [C1994/A28701].

Conflicts of Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.05.007.

References

[1] Sung H, et al., *Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.* CA: A Cancer Journal for Clinicians. n/a(n/a).
[2] Taunk NK, Haffty BG, Kostis JB, Goyal S. Radiation-induced heart disease: pathologic abnormalities and putative mechanisms. Front Oncol 2015;5 (39):1–8. https://doi.org/10.3389/fonc.2015.00039.

[3] Ewer MS, Yeh ET, *Cancer and the Heart*. 2013: PMPH-USA.
[4] Santoro F, Ieva R, Lupo P, Pellegrino PL, Correale M, Di Biase M, et al. Late calcification of the mitral-aortic junction causing transient complete atrio-ventricular block after mediastinal radiation of Hodgkin lymphoma: multimodal visualization. Int J Cardiol 2012;155:e49–50.
[5] Stewart FA, Seemann I, Hoving S, Russell NS. Understanding radiation-induced cardiovascular damage and strategies for intervention. Clin Oncol 2013;25:617–24.
[6] McWilliam A, Kennedy J, Hodgson C, Vasquez Osorio E, Faivre-Finn C, van Herk M. Radiation dose to heart base linked with poorer survival in lung cancer patients. Eur J Cancer 2017;85:106–13.
[7] Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. The Lancet. 2005 May 14; 365 (9472):1687–717.
[8] McGale P, Darby SC, Hall P, Adolfsson J, Bengtsson N-O, Bennet AM, et al. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. Radiother Oncol 2011;100:167–75.
[9] Cutter DJ et al. Risk of valvular heart disease after treatment for Hodgkin lymphoma. J Natl Cancer Inst 2015;107:djv008.
[10] van Nimwegen FA, Schaapveld M, Janus CPM, Krol ADG, Petersen EJ, Raemaekers JMM, et al. Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. JAMA Internal Med 2015;175:1007.
[11] van Nimwegen FA, Ntentas G, Darby SC, Schaapveld M, Hauptmann M, Lugtenburg PJ, et al. Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines. Blood 2017;129:2257–65.
[12] Nissen HD, Appelt AL. Improved heart, lung and target dose with deep inspiration breath hold in a large clinical series of breast cancer patients. Radiother Oncol 2013;106:28–32.
[13] Cella L, Liuzzi R, Magliulo M, Conson M, Camera L, Salvatore M, et al. Radiotherapy of large target volumes in Hodgkin's lymphoma: normal tissue sparing capability of forward IMRT versus conventional techniques. Radiat Oncol 2010;5:33.
[14] Wang K et al. Cardiac toxicity after radiotherapy for stage III non-small-cell lung cancer: pooled analysis of dose-escalation trials delivering 70 to 90 Gy. J Clin Oncol 2017;35:1387–94.
[15] Robnett TJ, Machtay M, Vines EF, McKenna MG, Algazy KM, McKenna WG. Factors predicting severe radiation pneumonitis in patients receiving definitive chemoradiation for lung cancer. Int J Radiat Oncol Biol Phys 2000;48:89–94.
[16] Fay M, Tan A, Fisher R, Mac Manus M, Wirth A, Ball D. Dose-volume histogram analysis as predictor of radiation pneumonitis in primary lung cancer patients treated with radiotherapy. Int J Radiat Oncol Biol Phys 2005;61:1355–63.
[17] Bar-Ad V, Ohri N, Werner-Wasik M. Esophagitis, treatment-related toxicity in non-small cell lung cancer. Rev Recent Clin Trials 2012;7:31–5.
[18] Baker S, Fairchild A. Radiation-induced esophagitis in lung cancer. Lung Cancer (Auckland, NZ) 2016;7:119–27.
[19] Werner-Wasik M, Yorke E, Deasy J, Nam J, Marks LB. Radiation dose-volume effects in the esophagus. Int J Radiat Oncol Biol Phys 2010;76:S86–93.
[20] Islam KMM, Jiang X, Anggondowati T, Lin G, Ganti AK. Comorbidity and survival in lung cancer patients. Cancer Epidemiol Biomark Prev 2015;24:1079–85.
[21] Dess RT et al. Cardiac events after radiation therapy: combined analysis of prospective multicenter trials for locally advanced non-small-cell lung cancer. J Clin Oncol 2017;35:1395–402.
[22] Bradley JD, Hu C, Komaki RR, Masters GA, Blumenschein GR, Schild SE, et al. Long-term results of NRG oncology RTOG 0617: standard-versus high-dose chemoradiotherapy with or without cetuximab for unresectable stage III non-small-cell lung cancer. J Clin Oncol 2020;38(7):706–14.
[23] Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol 2015;16:187–99.
[24] Atkins KM, Chaunzwa TL, Lamba N, Bitterman DS, Rawal B, Bredfeldt J, et al. Association of left anterior descending coronary artery radiation dose with major adverse cardiac events and mortality in patients with non-small cell lung cancer. JAMA Oncol 2021;7:206.
[25] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339: b2535.
[26] De Martino F, Clemente S, Graeff C, Palma G, Cella L. Dose calculation algorithms for external radiation therapy: an overview for practitioners. Appl Sci 2021;11:6806.
[27] Kadoya N, Cho SY, Kanai T, Onozato Y, Ito K, Dobashi S, et al. Dosimetric impact of 4-dimensional computed tomography ventilation imaging-based functional treatment planning for stereotactic body radiation therapy with 3-dimensional conformal radiation therapy. Pract Radiat Oncol 2015;5:e505–12.
[28] Della Gala G, Dirkx MLP, Hoekstra N, Fransen D, Lanconelli N, van de Pol M, et al. Fully automated VMAT treatment planning for advanced-stage NSCLC patients. Strahlenther Onkol 2017;193:402–9.
[29] Liu C, Schild SE, Chang JY, Liao Z, Korte S, Shen J, et al. Impact of spot size and spacing on the quality of robustly optimized intensity modulated proton therapy plans for lung cancer. Int J Radiat Oncol Biol Phys 2018;101:479–89.
[30] Gagliardi G, Constine LS, Moiseenko V, Correa C, Pierce LJ, Allen AM, et al. Radiation dose-volume effects in the heart. Int J Radiat Oncol Biol Phys 2010;76:S77–85.
[31] Jacob S, Camilleri J, Derreumaux S, Walker V, Lairez O, Lapeyre M, et al. Is mean heart dose a relevant surrogate parameter of left ventricle and coronary arteries exposure during breast cancer radiotherapy: a dosimetric evaluation based on individually-determined radiation dose (BACCARAT study). Radiat Oncol (London, England) 2019;14:29.
[32] Vyfhuis MAL, Onyeuku N, Diwanji T, Mossahebi S, Amin NP, Badiyan SN, et al. Advances in proton therapy in lung cancer. Ther Adv Respir Dis 2018;12:17537.
[33] Bradley JD et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol 2015;16:187–99.
[34] Brenner DJ, Shuryak I, Jozsef G, DeWyngaert KJ, Formenti SC. Risk and risk reduction of major coronary events associated with contemporary breast radiotherapy. JAMA Internal Med 2014;174:158.
[35] Ou S-H, Zell JA, Ziogas A, Anton-Culver H. Prognostic factors for survival of stage I nonsmall cell lung cancer patients. Cancer 2007;110:1532–41.
[36] Shien K, Toyooka S, Soh J, Hotta K, Katsui K, Oto T, et al. Lower lobe origin is a poor prognostic factor in locally advanced non-small-cell lung cancer patients treated with induction chemoradiotherapy. Mol Clin Oncol 2015;3:706–12.
[37] Wink KCJ, Roelofs E, Simone CB, Dechambre D, Santiago A, van der Stoep J, et al. Photons, protons or carbon ions for stage I non-small cell lung cancer – Results of the multicentric ROCOCO in silico study. Radiother Oncol 2018;128:139–46.
[38] Yang W et al. A dosimetric comparison of dose escalation with simultaneous integrated boost for locally advanced non-small-cell lung cancer. Biomed Res Int 2017;2017:9736362.
[39] Chun SG et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: A secondary analysis of the NRG oncology RTOG 0617 randomized clinical trial. J Clin Oncol 2017;35:56–62.
[40] Kim ST et al. Non-coplanar VMAT plans for lung SABR to reduce dose to the heart: a planning study. Br J Radiol 2020;93:20190596.
[41] Sanford L, Molloy J, Kumar S, Randall M, McGarry R, Pokhrel D. Evaluation of plan quality and treatment efficiency for single-isocenter/two-lesion lung stereotactic body radiation therapy. J Appl Clin Med Phys 2019;20:118–27.
[42] Huang B-T, Lin Z, Lin P-X, Lu J-Y, Chen C-Z. Monitor unit optimization in stereotactic body radiotherapy for small peripheral non-small cell lung cancer patients. Sci Rep 2016;5:18453.
[43] Hrbacek J, Lang S, Graydon SN, Klöck S, Riesterer O. Dosimetric comparison of flattened and unflattened beams for stereotactic ablative radiotherapy of stage I non-small cell lung cancer. Med Phys 2014;41:031709.
[44] Meijer TWH, Wijsman R, Usmanij EA, Schuurbiers OCJ, Kollenburg PV, Bouwmans L, et al. Stereotactic radiotherapy boost after definite chemoradiation for non-responding locally advanced NSCLC based on early response monitoring 18F-FDG-PET/CT. Phys Imag Radiat Oncol 2018;7:16–22.
[45] Xhaferllari I, El-Sherif O, Gaede S. Comprehensive dosimetric planning comparison for early-stage, non-small cell lung cancer with SABR: fixed-beam IMRT versus VMAT versus TomoTherapy. J Appl Clin Med Phys 2016;17:329–40.
[46] Han C, Schultheiss TE, Wong JYC. Estimation of radiation-induced secondary cancer risks for early-stage non-small cell lung cancer patients after stereotactic body radiation therapy. Pract Radiat Oncol 2017;7:e185–94.
[47] Vojtíšek R, Mužík J, Šlampa P, Budíková M, Hejsek J, Smolák P, et al. The impact of PET/CT scanning on the size of target volumes, radiation exposure of organs at risk, TCP and NTCP, in the radiotherapy planning of non-small cell lung cancer. Rep Pract Oncol Radiother 2014;19:182–90.
[48] De Ruysscher D et al. European Organization for Research and Treatment of Cancer (EORTC) recommendations for planning and delivery of high-dose, high precision radiotherapy for lung cancer. Radiother Oncol 2017;124(1):1–10.
[49] Vojtíšek R. Cardiac toxicity of lung cancer radiotherapy. Rep Pract Oncol Radiother 2020;25:13–9.