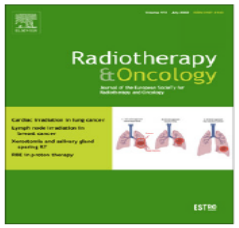
Radiotherapy and Oncology 172 (2022) 118–125

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

Maeve Kearney [a,*,1], Maeve Keys [b,c,1], Corinne Faivre-Finn [c], Zhe Wang [d], Marianne C Aznar [d,e,1], Frances Duane [b,f,g,1]

[a] *Applied Radiation Therapy Trinity, Discipline of Radiation Therapy, Trinity College Dublin;* [b] *St Luke's Radiation Oncology Network, St. Luke's Hospital, Dublin, Ireland;* [c] *The Christie NHS Foundation Trust, University of Manchester;* [d] *Nuffield Department of Population Health, University of Oxford;* [e] *Manchester Cancer Research Centre, Division of Cancer Sciences, Faculty of Biology, Medicine and Health, University of Manchester, United Kingdom;* [f] *School of Medicine, Trinity College Dublin; and* [g] *Trinity St James's Cancer Institute, St. James's Hospital, Dublin, Ireland*

Dr.Kaustav Talapatra

Director Radiation Oncology &

Coordinator Radiosurgery

Nanavati Max Super Specialty Hospital

INTRODUCTION

- 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

INTRODUCTION

- Given the poor prognosis traditionally associated with lung cancer, most toxicity studies have focused on acute radiation-related pneumonitis and oesophagitis.

- 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.

INTRODUCTION

- The RTOG 0617 reported an association between heart dose parameters (such as heart V5) and poorer overall survival.
- 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.
- In another study of patients with pre-existing cardiac disease MHDs of 5 and 12 Gy predicted grade 3 cardiac event rates of 10% and 15% respectively

AIMS

- present a systematic review of heart doses reported in in the modern era of lung cancer RT
  - heart dose variation according to region irradiated, laterality, treatment modality and planning technique.
- Summarize treatment strategies, such as motion management or use of particle therapies, which may lead to a reduction in heart dose.

MATERIALS AND METHODS

CONSORT DIAGRAM

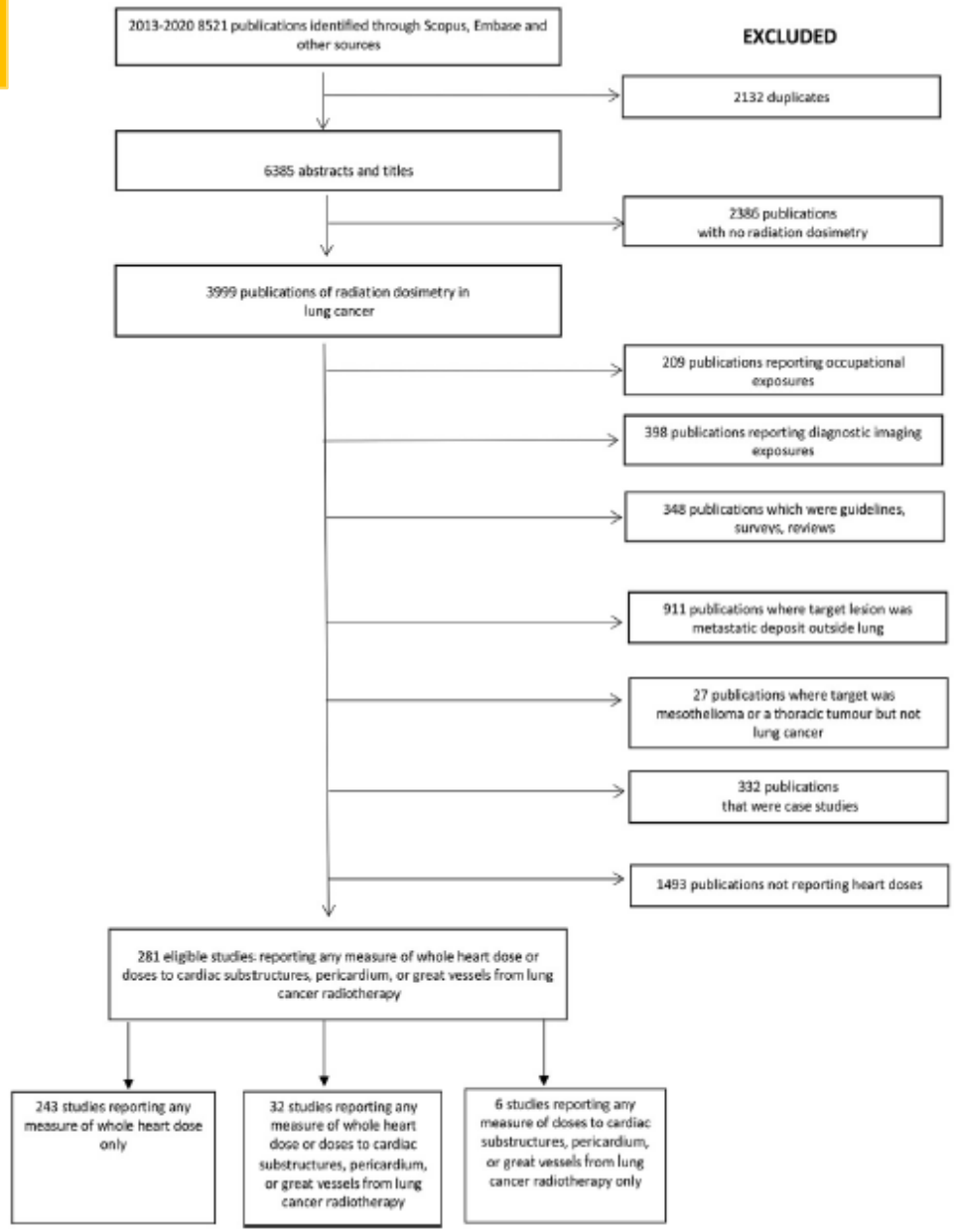


Fig. 1. The process of study identification for the review.

DATA EXTRACTION

Following were included:

- 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

DATA EXTRACTION

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)

(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)

RESPIRATORY MOTION MANAGEMENT

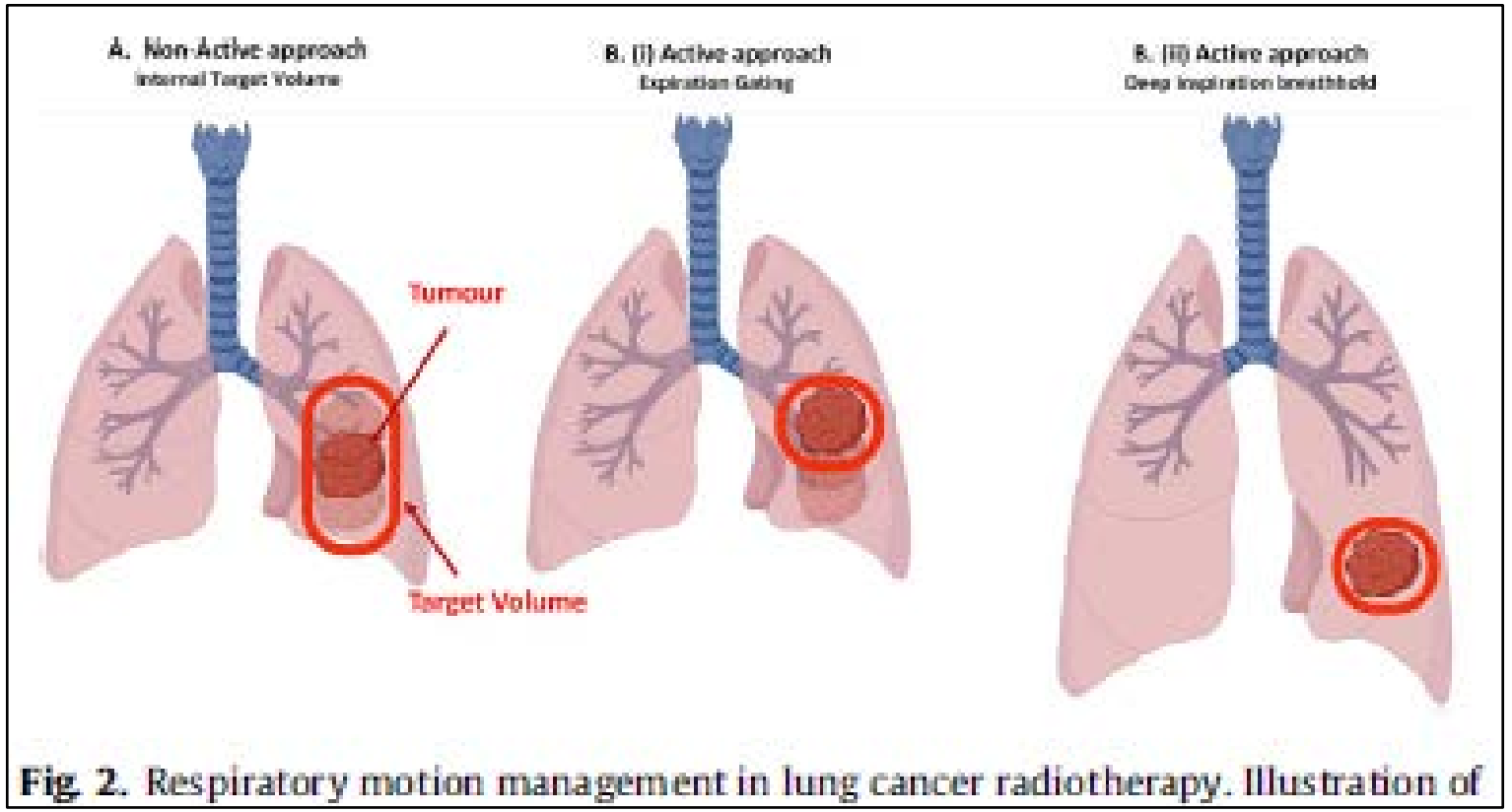


Fig. 2. Respiratory motion management in lung cancer radiotherapy. Illustration of

DATA EXTRACTION

- Dose optimizer 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 optimization.

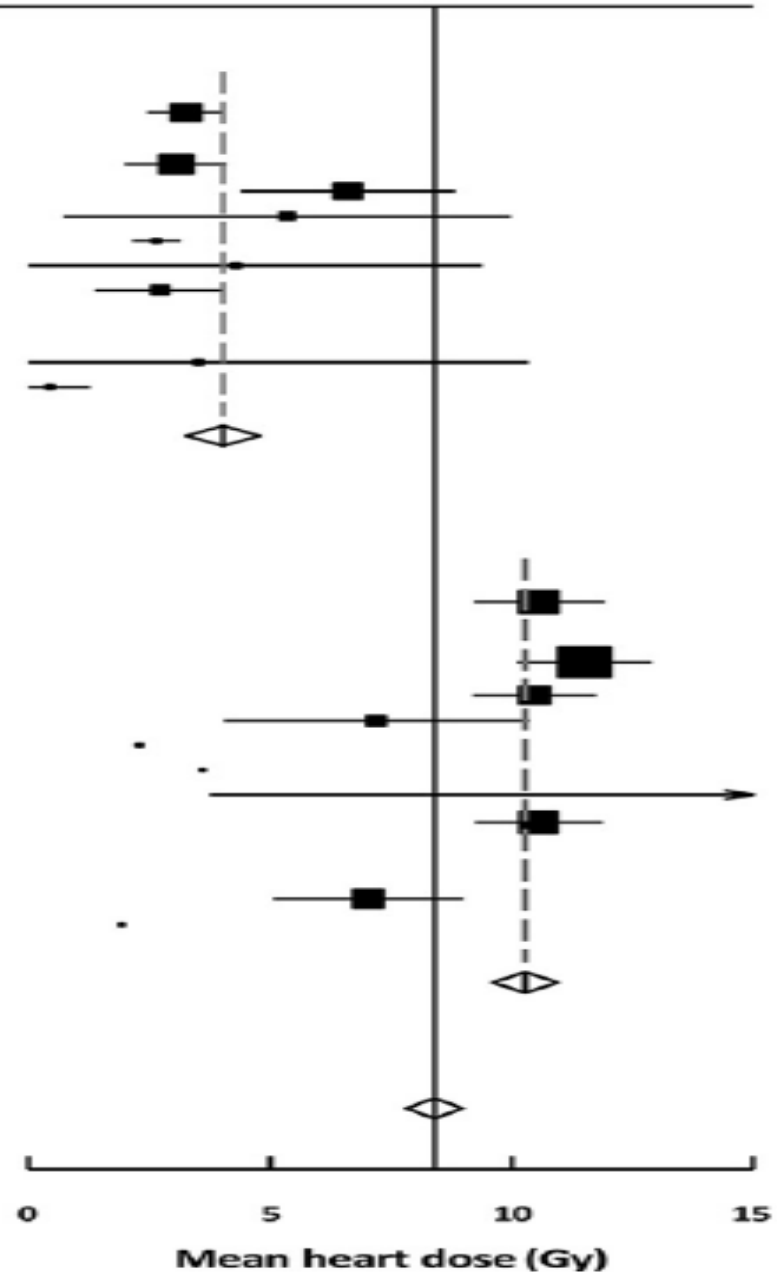
DATA ANALYSIS

- 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.

RESULTS

	Number of regimens	Mean heart dose (Gy) Average* (SE)	Range†	Average & 95% CI
(a) SABR		χ^2_8 = 43.3; p,0.001		
Photon Therapy	**(162)**	**4.1 (0.4)**	**<0.1–32.4**	
3DCRT	41	3.3 (0.4)	0.3–10.3	
IMRT	(108)	4.6 (0.6)	0.1–32.4	
Static Gantry IMRT	54	3.0 (0.5)	0.1–19.1	
Volumetric Modulated Arc Therapy	40	6.6 (1.1)	0.2–32.4	
Helical Tomotherapy	9	5.3 (2.4)	0.5–23.0	
Robotic Driven Delivery Systems	2	2.6 (0.3)	2.4–2.9	
IMRT not specified	3	4.3 (2.6)	1.6–9.5	
Other/not specified	13	2.7 (0.7)	<0.1–6.9	
Particle Therapy	**(6)**	**2.0 (1.7)**	**<0.1–10.5**	
Proton	3	3.5 (3.5)	<0.1–10.5	
Carbon–Ion	3	0.5 (0.4)	<0.1–1.3	
Subtotal	**168**	**4.0 (0.4)**	**<0.1–32.4**	
(b) non–SABR		χ^2_6 = 18.2; p=0.006		
Photon Therapy	**(343)**	**10.8 (0.4)**	**<0.1–48.4**	
3DCRT	76	10.6 (0.7)	<0.1–24.5	
IMRT	(198)	10.9 (0.5)	<0.1–48.4	
Static Gantry IMRT	135	11.5 (0.7)	<0.1–48.4	
Volumetric Modulated Arc Therapy	44	10.5 (0.7)	1.0–20.7	
Helical Tomotherapy	15	7.2 (1.6)	0.2–18.7	
DCAT	1	2.3	2.3–2.3	
Robotic Driven Delivery Systems	1	3.6	3.6–3.6	
IMRT not specified	2	15.1 (5.8)	9.3–20.9	
Other/not specified	69	10.6 (0.7)	0.3–22.3	
Particle Therapy	**(49)**	**6.9 (1.0)**	**<0.1–38.7**	
Proton	48	7.0 (1.0)	<0.1–38.7	
Carbon–Ion	1	1.9	1.9–1.9	
Subtotal	**392**	**10.3 (0.3)**	**<0.1–48.4**	
Total	**560**	**8.4 (0.3)**	**<0.1–48.4**	

Difference between (a) and (b): χ^2_1 = 145.4; 2p <0.001



Heart doses varied according to location and disease stage

SABR

- For SABR, MHD was higher in right-sided regimens (4.6 vs. 2.9 Gy
- 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).

NON SABR

- Exposure was not significantly different between left and right-sided tumours
- Average mean heart dose was 12.4 Gy (0–32.4) for Stage III disease

Table S2. Average mean whole heart doses reported in lung cancer radiotherapy published 2013-2020 according to laterality

Treatment Modality	Laterality	no. of regimens	mean	sd	min	max
SABR	Left[1]	60	2.9	4.9	0.1	32.4
	Right[2]	33	4.6	5.2	0.1	19.1
	Unspecified[3]	75	4.8	4.8	0	23
	All	**168**	**4**	**5**	**0**	**32.4**
non-SABR	Left[4]	27	8.4	5	1	21.9
	Right[5]	34	8.9	5.9	1	23.1
	Unspecified	331	10.6	7.1	0	48.4
	All	**392**	**10.3**	**6.9**	**0**	**48.4**
Total	**All**	**560**	**8.4**	**7**	**0**	**48.4**

Abbreviations: SABR : stereotactic ablative radiotherapy

All doses reported refer to physical dose

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**				

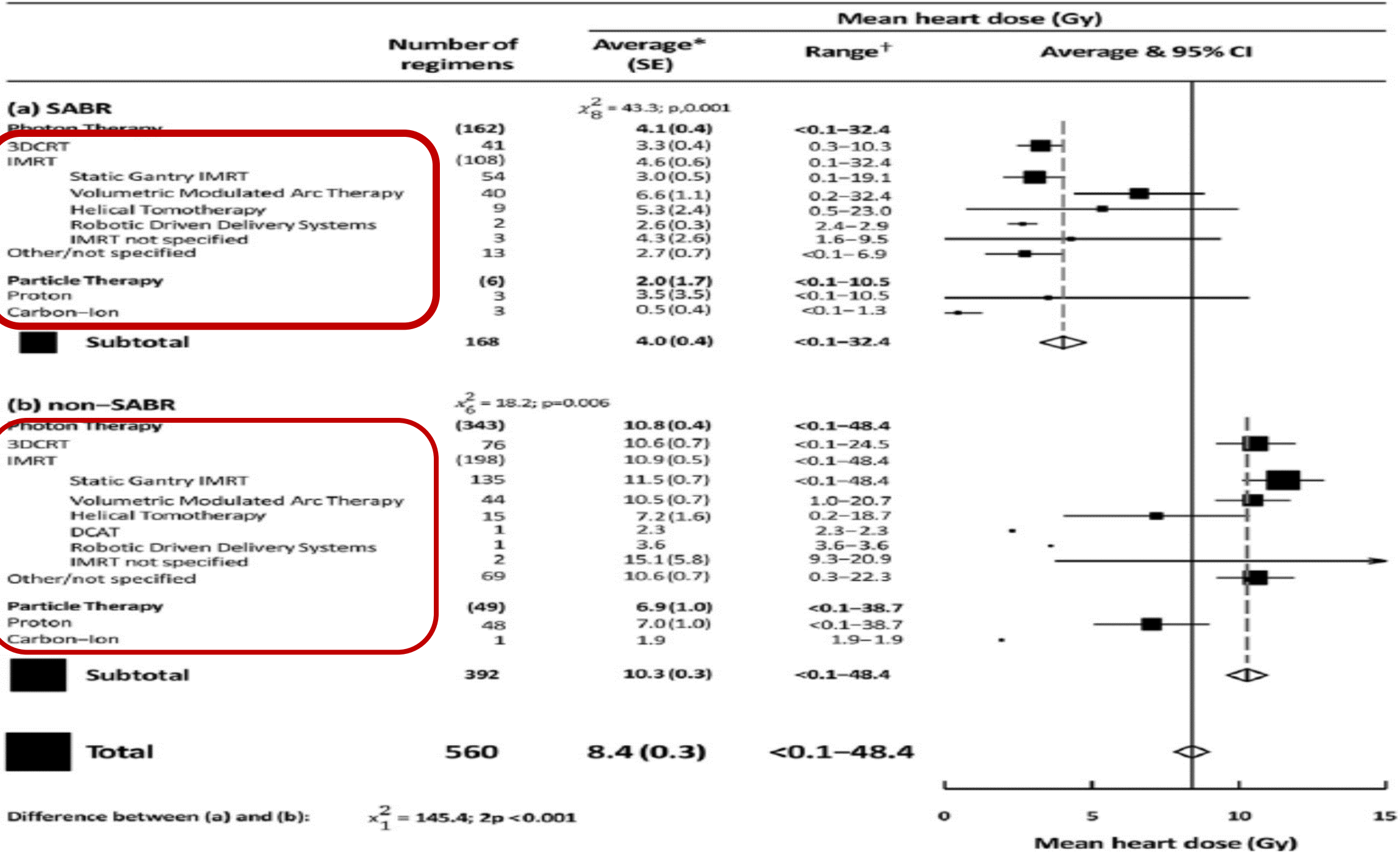
Heart doses varied according to radiation modality and treatment planning technique used

SABR REGIMEN

- 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.

NON SABR Regimen

- 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)


Mean heart dose (Gy)
Number of regimens
Average* (SE)
Range†
Average & 95% CI
(a) SABR
χ^2_8 = 43.3; p,0.001
Photon Therapy (162) 4.1 (0.4) <0.1–32.4
3DCRT 41 3.3 (0.4) 0.3–10.3
IMRT (108) 4.6 (0.6) 0.1–32.4
Static Gantry IMRT 54 3.0 (0.5) 0.1–19.1
Volumetric Modulated Arc Therapy 40 6.6 (1.1) 0.2–32.4
Helical Tomotherapy 9 5.3 (2.4) 0.5–23.0
Robotic Driven Delivery Systems 2 2.6 (0.3) 2.4–2.9
IMRT not specified 3 4.3 (2.6) 1.6–9.5
Other/not specified 13 2.7 (0.7) <0.1–6.9
Particle Therapy (6) 2.0 (1.7) <0.1–10.5
Proton 3 3.5 (3.5) <0.1–10.5
Carbon–Ion 3 0.5 (0.4) <0.1–1.3
Subtotal 168 4.0 (0.4) <0.1–32.4
(b) non–SABR
χ^2_6 = 18.2; p=0.006
Photon Therapy (343) 10.8 (0.4) <0.1–48.4
3DCRT 76 10.6 (0.7) <0.1–24.5
IMRT (198) 10.9 (0.5) <0.1–48.4
Static Gantry IMRT 135 11.5 (0.7) <0.1–48.4
Volumetric Modulated Arc Therapy 44 10.5 (0.7) 1.0–20.7
Helical Tomotherapy 15 7.2 (1.6) 0.2–18.7
DCAT 1 2.3 2.3–2.3
Robotic Driven Delivery Systems 1 3.6 3.6–3.6
IMRT not specified 2 15.1 (5.8) 9.3–20.9
Other/not specified 69 10.6 (0.7) 0.3–22.3
Particle Therapy (49) 6.9 (1.0) <0.1–38.7
Proton 48 7.0 (1.0) <0.1–38.7
Carbon–Ion 1 1.9 1.9–1.9
Subtotal 392 10.3 (0.3) <0.1–48.4
Total 560 8.4 (0.3) <0.1–48.4
Difference between (a) and (b): χ^2_1 = 145.4; 2p <0.001
0
5
10
15
Mean heart dose (Gy)

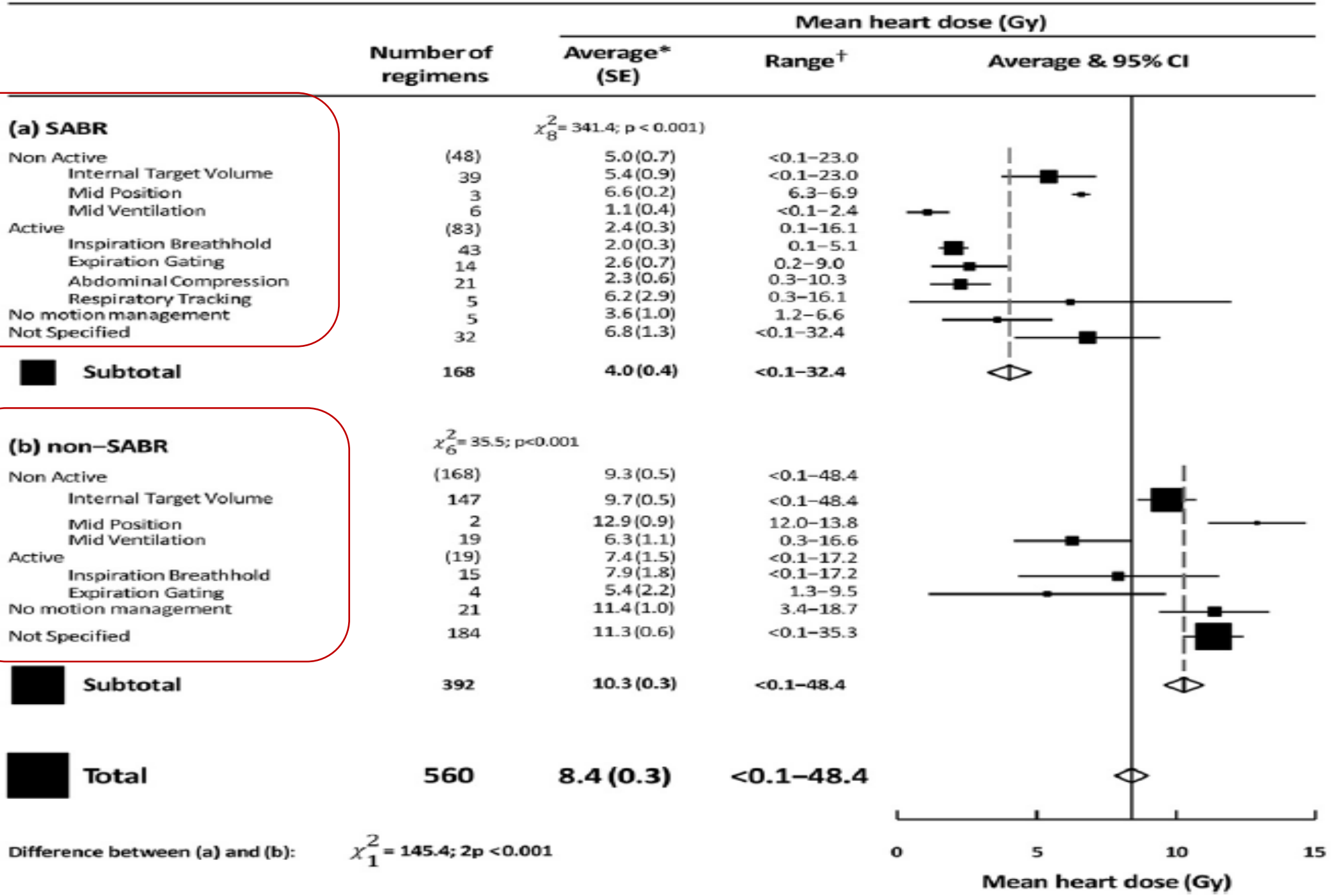
Heart doses varied according to respiratory motion management

For SABR

- 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)).

NON-SABR

- 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.


Mean heart dose (Gy)
Number of regimens
Average* (SE)
Range†
Average & 95% CI
(a) SABR
χ^2_8= 341.4; p < 0.001)
Non Active (48) 5.0 (0.7) <0.1–23.0
Internal Target Volume 39 5.4 (0.9) <0.1–23.0
Mid Position 3 6.6 (0.2) 6.3–6.9
Mid Ventilation 6 1.1 (0.4) <0.1–2.4
Active (83) 2.4 (0.3) 0.1–16.1
Inspiration Breathhold 43 2.0 (0.3) 0.1–5.1
Expiration Gating 14 2.6 (0.7) 0.2–9.0
Abdominal Compression 21 2.3 (0.6) 0.3–10.3
Respiratory Tracking 5 6.2 (2.9) 0.3–16.1
No motion management 5 3.6 (1.0) 1.2–6.6
Not Specified 32 6.8 (1.3) <0.1–32.4
Subtotal 168 4.0 (0.4) <0.1–32.4
(b) non–SABR
χ^2_6= 35.5; p<0.001
Non Active (168) 9.3 (0.5) <0.1–48.4
Internal Target Volume 147 9.7 (0.5) <0.1–48.4
Mid Position 2 12.9 (0.9) 12.0–13.8
Mid Ventilation 19 6.3 (1.1) 0.3–16.6
Active (19) 7.4 (1.5) <0.1–17.2
Inspiration Breathhold 15 7.9 (1.8) <0.1–17.2
Expiration Gating 4 5.4 (2.2) 1.3–9.5
No motion management 21 11.4 (1.0) 3.4–18.7
Not Specified 184 11.3 (0.6) <0.1–35.3
Subtotal 392 10.3 (0.3) <0.1–48.4
Total 560 8.4 (0.3) <0.1–48.4
Difference between (a) and (b): χ^2_1 = 145.4; 2p <0.001
0
5
10
15
Mean heart dose (Gy)

DISCUSSION

- 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

DISCUSSION

Heart radiation doses (physical doses) were much less for SABR than non-SABR regimens (MHD 4.0 (range < 0.1–32.4) vs 10.3 Gy (range < 0.1–48.4)).

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 SABR, exposure was higher in central and lower lobe lesions (6.3 and 5.8 Gy respectively) compared to other locations.

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).

DISCUSSION

- 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
- Studies emphasized using partial arcs to reduce contralateral lung dose and planning optimization to specifically reduce pneumonitis and secondary breast cancer risk

SABR PATIENTS

- Particle therapy, specifically C-Ion, reduced mean and maximum heart doses in early stage SABR patients.
- 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

NON SABR PATIENTS

- 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.

STRENGTHS

First systematic review of heart doses in lung cancer RT

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 tumor size has on treatment planning technique chosen and associated cardiac exposure

FUTURE

The need to identify specific cardiac substructures and dose volume relationships to improve cardiac risk estimation is consistently cited

CONCLUSION

- **For photon based IMRT, the most common technique used in the clinic, more stringent planning optimization 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**
- **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**

THANK YOU