# **Supplemental Online Content**

Zhou P, Du Y, Zhang Y, et al. Efficacy and safety in proton therapy and photon therapy for patients with esophageal cancer: a meta-analysis. *JAMA Netw Open*. 2023;6(8):e2328136. doi:10.1001/jamanetworkopen.2023.28136

eAppendix. Literature Search Strategy

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This supplemental material has been provided by the authors to give readers additional information about their work.

## eAppendix. Literature Search Strategy

### PubMed

#1. "Esophageal Neoplasms" [Mesh]

#3. #1 OR #2

#4. "Proton Therapy"[Mesh]

#5. ((((((Proton Therapies) OR (Therapies, Proton)) OR (Therapy, Proton)) OR (Proton Beam Therapy)) OR (Proton Beam Therapies)) OR (Therapies, Proton Beam)) OR (Therapy, Proton Beam)) OR (Proton Beam)) OR (Prot

#6. #4 OR #5

#7. #3 AND #6

#### Embase

#1. 'esophagus cancer'/exp

#2. 'esophag\* neoplasm\*' OR 'neoplasm\*, esophag\*' OR 'cancer of esophag\*' OR 'esophag\* cancer\*' OR 'cancer\*, esophag\*' OR 'cancer\* of the esophag\*'

#3. #1 OR #2

#4. 'proton therapy'/exp

#5. 'proton therap\*' OR 'therap\*, proton' OR 'proton beam therap\*' OR 'therap\*, proton beam' OR 'proton beam radiation therap\*'

#6. #4 OR #5

#7. #3 AND #6

Cochrane

#1. MeSH descriptor: [Esophageal Neoplasms] explode all trees

#2. ('esophag\* neoplasm\*' OR 'neoplasm\*, esophag\*' OR 'cancer of esophag\*' OR 'esophag\* cancer\*' OR 'cancer\*, esophag\*' OR 'cancer\* of the esophag\*'):ti,ab,kw

#3. #1 OR #2

#4. MeSH descriptor: [Proton Therapy] explode all trees

#5. ('proton therap\*' OR 'therap\*, proton' OR 'proton beam therap\*' OR 'therap\*, proton beam' OR 'proton beam radiation therap\*'):ti,ab,kw

#6. #4 OR #5

#8. #3 AND #6

Web of science

#1. TS= esophag\*

#2. TS= (cancer\* OR tumor\* OR neoplasm\*)

#3. #1 AND #2

#4. TS= (proton therap\*) OR (therap\*, proton) OR (proton beam therap\*) OR (therap\*, proton beam) OR (proton beam radiation therap\*) #5. #3 AND #4

TS=Topic Search in: Web of Science Core Collection.

Link:

https://www.webofscience.com/wos/woscc/summary/ae4b2cf6-c13f-48e9-949a-0ea1fb714582-6e1f3b8e/relevance/1

Sinomed

#1. "食管肿瘤"[全部字段:智能] OR "食管癌"[全部字段:智能] OR "食道肿瘤"[全部字段:智能] OR "食道癌"[全部字段:智能] #2. "质子治疗"[全部字段:智能] OR "质子放疗"[全部字段:智能] OR "质子"[全部字段:智能] #3. #1 AND #2

CNKI

(TKA % '食管肿瘤' OR TKA % '食管癌' OR TKA % '食道肿瘤' OR TKA % '食道癌') AND (TKA % '质子治疗' OR TKA % '质子' OR TKA % '质子放疗')

TKA: 篇关摘; %: 模糊检索

# eFigure 1. Forest Plots of Dose-Volume Parameters for OARs With Proton vs Photon Therapy

a) Lung-D<sub>mean</sub>

	P	roton	1	PI	notor	n		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
1.2.1 vs. 3D-CRT							-		
Hirano et al. 16 (2018)	5.8	2.2	27	8.2	2.1	27	4.7%	-2.40 [-3.55, -1.25]	
Lin et al. 37 (2017)	6.1	2.6	111	10.5	3.9	214	4.9%	-4.40 [-5.11, -3.69]	-
Ling et al. 20 (2014)	6	2.6	10	9.4	4	10	3.4%	-3.40 [-6.36, -0.44]	
Subtotal (95% CI)			148			251	13.1%	-3.46 [-5.03, -1.88]	◆
Heterogeneity: Tau <sup>2</sup> = 1.33	3; Chi² =	8.51,	df = 2	(P = 0.0	)1); l <sup>a</sup>	<sup>2</sup> = 77%			
Test for overall effect: Z =	4.31 (P	< 0.00	001)						
1.2.2 vs. IMRT									
Bhangoo et al. 31 (2020)	4.1	1.5	32	8.4	6.2	32	4.0%	-4.30 [-6.51, -2.09]	
Cui et al. 52 (2022)	4.2	1.9	30	12.6	3.8	30	4.5%	-8.40 [-9.92, -6.88]	_ <b>_</b>
Hirano et al. 16 (2018)	5.8	2.2	27	9.5	2.2	27	4.7%	-3.70 [-4.87, -2.53]	
Lin et al. 28 (2020)	4.9	1.9	46	8.9	3.6	61	4.8%	-4.00 [-5.06, -2.94]	- <b>-</b>
Lin et al. 37 (2017)	6.1	2.6	111	9.5	3.2	255	5.0%	-3.40 [-4.02, -2.78]	-
∟ing et al. 20 (2014)	6	2.6	10	9.5	3.2	10	3.7%	-3.50 [-6.06, -0.94]	
Mu et al. 23 (2011)	7.3	1.8	10	12.1	1.8	10	4.5%	-4.80 [-6.38, -3.22]	
Møller et al. 15 (2019)	3.3	1.9	26	8.8	3.8	26	4.4%	-5.50 [-7.13, -3.87]	
Nelsh et al. 21 (2011)	4.9	2.2	10	8.3	3.2	10	3.8%	-3.40 [-5.81, -0.99]	
(i et al. 35 (2017)	6.5	3.2	132	10	3.3	211	4.9%	-3.50 [-4.20, -2.80]	-
Zhang et al. 11 (2021)	10.3	6	25	12.3	6.2	25	3.1%	-2.00 [-5.38, 1.38]	
Zhang et al. 22 (2008)	6.8	1.4	15	9.8	1.8	15	4.7%	-3.00 [-4.15, -1.85]	
Zhang et al. 51 (2022)	3.8	0.7	11	14.1	2.8	11	4.4%	-10.30 [-12.01, -8.59]	
Subtotal (95% CI)			485			723	56.5%	-4.66 [-5.70, -3.61]	◆
Heterogeneity: Tau <sup>2</sup> = 2.94	l; Chi² =	98.71	1, df = 1	2 (P <	0.000	001); l <sup>2</sup> :	= 88%		
Test for overall effect: Z =	8.74 (P	< 0.00	0001)						
1.2.3 vs. VMAT									
Anakotta et al. 12 (2020)	4.1	1.6	19	9	3.5	19	4.3%	-4.90 [-6.63, -3.17]	
Celik et al. 13 (2020)	2.9	1.2	20	8.6	2.9	20	4.6%	-5.70 [-7.08, -4.32]	<u> </u>
Cui et al. 52 (2022)	4.2	1.9	30	11.5	3.5	30	4.6%	-7.30 [-8.73, -5.87]	
(ato et al. 50 (2022)	2.1	0.7	10	2.2	0.7	10	5.0%	-0.10 [-0.71, 0.51]	+
_iu et al. 14 (2019)	4.3	2.3	19	8.17	2.9	16	4.3%	-3.87 [-5.63, -2.11]	
Warren et al. 19 (2016)	6.7	2.2	21	13.5	2.6	21	4.5%	-6.80 [-8.26, -5.34]	<b>—</b>
Zhang et al. 11 (2021)	10.3	6	25	12.3	5.9	25	3.2%	-2.00 [-5.30, 1.30]	
Subtotal (95% CI)			144			141	30.5%	-4.41 [-7.14, -1.68]	
Heterogeneity: Tau <sup>2</sup> = 12.7	76; Chi² :	= 165	.79, df	= 6 (P <	0.00	0001); ľ	² = 96%		
Test for overall effect: Z =	3.17 (P =	= 0.00	02)	-					
Total (95% CI)			777			1115	100.0%	-4.42 [-5.38, -3.47]	•
Heterogeneity: Tau <sup>2</sup> = 4.69	; Chi² =	298.7	78. df =	22 (P <	0.00	0001); P	<sup>2</sup> = 93%		
Test for overall effect: Z =	9.07 (P	< 0.00	0001)	- 1.		,, .			-10 -5 0 5 10
Fest for subaroup difference	ces: Chi <sup>2</sup>	= 1.5	57. df =	2 (P =	0.46)	$I^2 = 0.9$	6		Proton Photon

# b) Lung-V<sub>5</sub>

	Р	Proton Photon						Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV. Random, 95% Cl		
1.1.1 vs. 3D-CRT											
Hirano et al. 16 (2018)	25.2	10.8	27	33.1	8.8	27	5.9%	-7.90 [-13.15, -2.65]			
Ling et al. 20 (2014)	21.4	10.3	10	34.1	13.9	10	5.2%	-12.70 [-23.42, -1.98]			
Subtotal (95% CI)			37			37	11.1%	-8.83 [-13.55, -4.11]	$\bullet$		
Heterogeneity: Tau <sup>2</sup> = 0.00	; Chi² =	0.62, 0	df = 1 (F	<b>P</b> = 0.43	3); I² =	0%					
Test for overall effect: Z =	3.67 (P :	= 0.000	02)								
1.1.2 vs. IMRT											
Cui et al. 52 (2022)	14.2	5.4	30	55	18.4	30	5.7%	-40.80 [-47.66, -33.94]			
Hirano et al. 16 (2018)	25.2	10.8	27	45.2	10.5	27	5.8%	-20.00 [-25.68, -14.32]			
Lin et al. 28 (2020)	21.2	8.4	46	44.8	16.9	61	5.9%	-23.60 [-28.49, -18.71]			
Ling et al. 20 (2014)	21.4	10.3	10	46.9	17.6	10	5.0%	-25.50 [-38.14, -12.86]			
Mu et al. 23 (2011)	19.4	4.3	10	50.8	11	10	5.7%	-31.40 [-38.72, -24.08]			
Møller et al. 15 (2019)	10.7	6	26	42.8	15.1	26	5.8%	-32.10 [-38.35, -25.85]			
Welsh et al. 21 (2011)	19	6.3	10	38	15.8	10	5.3%	-19.00 [-29.54, -8.46]			
Xi et al. 35 (2017)	28.4	14.1	132	48.1	14.7	211	6.0%	-19.70 [-22.82, -16.58]	-		
Zhang et al. 11 (2021)	32.7	18.2	25	50.8	23.7	25	5.1%	-18.10 [-29.81, -6.39]			
Zhang et al. 22 (2008)	31.8	5.9	15	49.6	8.9	15	5.9%	-17.80 [-23.20, -12.40]	-		
Zhang et al. 51 (2022)	20.5	3.9	11	71.2	17.9	11	5.2%	-50.70 [-61.53, -39.87]	<b>•</b>		
Subtotal (95% CI)			342			436	61.4%	-26.89 [-32.19, -21.58]	•		
Heterogeneity: Tau <sup>2</sup> = 64.5	3; Chi² :	= 72.93	3, df = 1	0 (P <	0.0000	1);   <sup>2</sup> =	86%				
Test for overall effect: Z =	9.93 (P ·	< 0.000	001)								
1.1.3 vs. VMAT											
Anakotta et al. 12 (2020)	<b>21</b> .1	8.6	19	53.7	20.1	19	5.4%	-32.60 [-42.43, -22.77]			
Cui et al. 52 (2022)	14.2	5.4	30	58	17.9	30	5.7%	-43.80 [-50.49, -37.11]			
Kato et al. 50 (2022)	9.7	3.5	10	9.8	3.4	10	6.0%	-0.10 [-3.12, 2.92]	+		
Liu et al. 14 (2019)	16.7	8.1	19	47.6	18.9	16	5.4%	-30.90 [-40.85, -20.95]			
Zhang et al. 11 (2021)	32.7	18.2	25	55.5	25.3	25	5.0%	-22.80 [-35.02, -10.58]			
Subtotal (95% Cl)			103			100	27.5%	-25.93 [-47.42, -4.45]			
Heterogeneity: Tau <sup>2</sup> = 580.	.25; Chi²	² = 179	.67, df :	= 4 (P <	0.000	101); l²:	= 98%				
Test for overall effect: Z = 2	2.37 (P =	= 0.02)	)								
Total (95% CI)			482			573	100.0%	-24 81 [-31 40 -18 21]			



	Pi	roton	n Photon					Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI
1.3.1 vs. 3D-CRT							_		
Hirano et al. 16 (2018)	21.3	9.1	27	25.7	7.5	27	9.8%	-4.40 [-8.85, 0.05]	
Ling et al. 20 (2014)	19.4	8.6	10	29.1	12.7	10	6.8%	-9.70 [-19.21, -0.19]	
Subtotal (95% CI)			37			37	16.5%	-5.35 [-9.38, -1.32]	$\bullet$
Heterogeneity: Tau <sup>2</sup> = 0	.00; Chi²	= 0.98	3, df = 1	(P = 0.	.32); l²	= 0%			
Test for overall effect: Z	= 2.60 (F	P = 0.0	09)						
1.3.2 vs. IMRT									
Cui et al. 52 (2022)	11.7	4.8	30	38.3	14.9	30	9.1%	-26.60 [-32.20, -21.00]	
Hirano et al. 16 (2018)	21.3	9.1	27	30	6.8	27	9.9%	-8.70 [-12.98, -4.42]	
Ling et al. 20 (2014)	19.4	8.6	10	37.8	14.7	10	6.2%	-18.40 [-28.96, -7.84]	
Welsh et al. 21 (2011)	15	6.3	10	23	9.5	10	8.2%	-8.00 [-15.07, -0.93]	
Xi et al. 35 (2017)	23.2	11.4	132	32.3	11.3	211	10.7%	-9.10 [-11.57, -6.63]	-
Zhang et al. 11 (2021)	28.8	16	25	39.8	20.6	25	6.4%	-11.00 [-21.22, -0.78]	
Zhang et al. 22 (2008)	23.8	7.1	15	33.9	8.1	15	9.2%	-10.10 [-15.55, -4.65]	
Subtotal (95% CI)			249			328	59.7%	-12.87 [-17.91, -7.83]	$\bullet$
Heterogeneity: Tau <sup>2</sup> = 3	5.07; Chi	² = 35	.84, df :	= 6 (P <	: 0.000	01); l² :	= 83%		
Test for overall effect: Z	= 5.01 (F	<b>&gt;</b> < 0.0	0001)						
1.3.3 vs. VMAT									
Cui et al. 52 (2022)	11.7	4.8	30	35.6	17.1	30	8.7%	-23.90 [-30.26, -17.54]	
Kato et al. 50 (2022)	7	2.6	10	18	8.1	10	9.3%	-11.00 [-16.27, -5.73]	<b>_</b> _
Zhang et al. 11 (2021)	28.8	16	25	47	24.1	25	5.8%	-18.20 [-29.54, -6.86]	
Subtotal (95% CI)			65			65	23.8%	-17.51 [-26.57, -8.45]	
Heterogeneity: Tau <sup>2</sup> = 4	8.90; Chi	² = 9.4	7, df =	2 (P = 0	0.009)	; l² = 79	%		
Test for overall effect: Z	= 3.79 (F	P = 0.0	002)						
Total (95% CI)			351			430	100.0%	-12.92 [-16.84, -9.00]	◆
Heterogeneity: Tau <sup>2</sup> = 3	5.66; Chi	<sup>2</sup> = 61	.73, df :	= 11 (P	< 0.00	001); l <sup>2</sup>	= 82%	-	
Test for overall effect: Z	= 6.46 (F	P < 0.0	00001)			1.			-20 -10 0 10 20
Test for subaroup differe	ences: Ch	ni² = 8	.77. df :	= 2 (P =	0.01)	l² = 77	.2%		Proton Photon

# d) Lung-V $_{20}$

	Р	roton		Р	hoton			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV. Random, 95% CI
1.4.1 vs. 3D-CRT									
Hirano et al. 16 (2018)	11.7	5.2	27	17	5.6	27	5.3%	-5.30 [-8.18, -2.42]	_ <b>—</b>
Ling et al. 20 (2014)	15.3	6.5	10	22.1	10.8	10	2.7%	-6.80 [-14.61, 1.01]	
Subtotal (95% CI)			37			37	8.0%	-5.48 [-8.18, -2.78]	$\bullet$
Heterogeneity: Tau <sup>2</sup> = 0.00	); Chi² =	0.12, c	if = 1 (F	> = 0.72	?);   <sup>2</sup> =	0%			
Test for overall effect: Z =	3.97 (P <	< 0.000	)1)		,, .				
			,						
1.4.2 vs. IMRT									
Bhangoo et al. 31 (2020)	10	4.7	32	12.3	5.4	32	5.5%	-2.30 [-4.78, 0.18]	
Cui et al. 52 (2022)	8.7	4.1	30	24.2	8.4	30	5.0%	-15.50 [-18.84, -12.16]	
Hirano et al. 16 (2018)	11.7	5.2	27	17.8	5.2	27	5.3%	-6.10 [-8.87, -3.33]	
Lin et al. 28 (2020)	8.7	3.1	46	14.1	7.9	61	5.6%	-5.40 [-7.58, -3.22]	
Ling et al. 20 (2014)	15.3	6.5	10	16.2	5.8	10	3.9%	-0.90 [-6.30, 4.50]	
Mu et al. 23 (2011)	14.8	3.5	10	20.9	3.1	10	5.3%	-6.10 [-9.00, -3.20]	
Møller et al. 15 (2019)	7.5	4.2	26	14.3	7.3	26	5.1%	-6.80 [-10.04, -3.56]	
Welsh et al. 21 (2011)	11	6.3	10	14	6.3	10	3.8%	-3.00 [-8.52, 2.52]	
Xi et al. 35 (2017)	11.3	6.1	132	18.4	7.7	211	5.9%	-7.10 [-8.57, -5.63]	-
Zhang et al. 11 (2021)	21.4	12.8	25	27.4	16.5	25	2.6%	-6.00 [-14.19, 2.19]	
Zhang et al. 22 (2008)	10.8	3.2	15	16.8	4.8	15	5.3%	-6.00 [-8.92, -3.08]	
Zhang et al. 51 (2022)	5.7	1.8	11	24.4	5	11	5.1%	-18.70 [-21.84, -15.56]	
Subtotal (95% CI)			374			468	58.5%	-7.16 [-9.77, -4.55]	◆
Heterogeneity: Tau <sup>2</sup> = 17.6	58; Chi² =	= 102.1	6, df =	11 (P <	0.000	001); l²	= 89%		
Test for overall effect: Z =	5.38 (P <	< 0.000	001)						
1.4.3 vs. VMAT									
Anakotta et al. 12 (2020)	6.5	3.6	19	12.1	7.5	19	4.8%	-5.60 [-9.34, -1.86]	
Celik et al. 13 (2020)	5.9	2.6	20	10.5	5.6	20	5.4%	-4.60 [-7.31, -1.89]	
Cui et al. 52 (2022)	8.7	4.1	30	17.6	8	30	5.1%	-8.90 [-12.12, -5.68]	
Kato et al. 50 (2022)	3.2	1.2	10	8.5	4.2	10	5.4%	-5.30 [-8.01, -2.59]	
Liu et al. 14 (2019)	8.5	5.2	19	9.1	5.3	16	4.9%	-0.60 [-4.09, 2.89]	
Warren et al. 19 (2016)	7.5	4	21	16.3	6.4	21	5.1%	-8.80 [-12.03, -5.57]	
Zhang et al. 11 (2021)	21.4	12.8	25	25.2	14.8	25	2.8%	-3.80 [-11.47, 3.87]	
Subtotal (95% CI)			144			141	33.5%	-5.55 [-7.71, -3.38]	◆
Heterogeneity: Tau <sup>2</sup> = 5.15	5; Chi² =	16.47,	df = 6	(P = 0.0)	)1); l² =	= 64%			
Test for overall effect: Z =	5.02 (P <	< 0.000	001)						
Total (05% CI)			EEF			646	100.0%	6 62 [ 9 24 4 70]	•
Hotar (95% CI)	0. 01:2	400.0	- 360	20 (P		040	- 0.4%	-0.32 [-0.24, -4.79]	<b>▼</b>
Test for everall effects 7 = 12.4	+9; Uni <sup>2</sup> =	= 123.3	90, ar =	20 (P <	0.000	JUT); 1²	= 84%		-20 -10 0 10 20
Test for overall effect: Z =	7.40 (P <	- 1.07	101) 7 ar - 7	VD - 0	EQ) 12	- 00/			Proton Photon
rest for subaroup difference	ces: Uni <sup>2</sup>	= 1.07	. at = 2	(P = 0)	.581. I*	= 0%			

e) Lung-V<sub>30</sub>

	Pr	roton		Photon				Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl		
1.5.1 vs. 3D-CRT							-				
Ling et al. 20 (2014)	6.1	2.9	10	9.8	5.1	10	16.9%	-3.70 [-7.34, -0.06]			
Subtotal (95% CI)			10			10	16.9%	-3.70 [-7.34, -0.06]			
Heterogeneity: Not applie	cable										
Test for overall effect: Z	= 1.99 (	P = 0	.05)								



# f) Lung-V<sub>40</sub>

	P	rotor	1	Pł	notor	1		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.6.1 vs. 3D-CRT									
Ling et al. 20 (2014)	4.3	2.1	10	4.7	2.9	10	7.4%	-0.40 [-2.62, 1.82]	
Subtotal (95% CI)			10			10	7.4%	-0.40 [-2.62, 1.82]	
Heterogeneity: Not app	olicable								
Test for overall effect:	Z = 0.35	5 (P =	0.72)						
1.6.2 vs. IMRT									
Ling et al. 20 (2014)	4.3	2.1	10	3.5	2	10	11.3%	0.80 [-1.00, 2.60]	
Subtotal (95% CI)			10			10	11.3%	0.80 [-1.00, 2.60]	
Heterogeneity: Not app	olicable								
Test for overall effect:	Z = 0.87	′ (P =	: 0.38)						
1.6.3 vs. VMAT									
Kato et al. 50 (2022)	1.1	0.6	10	1.5	0.9	10	81.3%	-0.40 [-1.07, 0.27]	
Subtotal (95% CI)			10			10	81.3%	-0.40 [-1.07, 0.27]	<b>•</b>
Heterogeneity: Not app	olicable								
Test for overall effect:	Z = 1.17	' (P =	0.24)						
Total (95% CI)			30			30	100.0%	-0.26 [-0.87, 0.34]	•
Heterogeneity: Chi <sup>2</sup> = <sup>2</sup>	1.52, df	= 2 (F	P = 0.4	7); l² = 0	)%			_	
Test for overall effect:	Z = 0.86	6 (P =	: 0.39)	-					-4 -2 U 2 4 Proton Photon
Test for subaroup diffe	rences:	Chi <sup>2</sup>	= 1.52.	df = 2 (	P = 0	).47). l²	= 0%		FIOLON Photon

# g) Heart-MLD

	Р	roton		Photon				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV. Random, 95% Cl
2.1.1 vs. 3D-CRT									
Hirano et al. 16 (2018)	17.6	9.7	27	31	11.5	27	3.3%	-13.40 [-19.07, -7.73]	
Lin et al. 37 (2017)	13.2	5.2	111	28.4	7.4	214	5.4%	-15.20 [-16.59, -13.81]	-
Ling et al. 20 (2014)	12.6	3.9	10	27.5	5.2	10	4.1%	-14.90 [-18.93, -10.87]	
Subtotal (95% CI)			148			251	12.8%	-15.08 [-16.36, -13.80]	•
Heterogeneity: Tau <sup>2</sup> = 0.00	0; Chi² =	0.37,	df = 2	(P = 0.8	3); l² =	= 0%			
Test for overall effect: Z =	23.15 (P	< 0.0	0001)						
2.1.2 vs. IMRT									
Bhangoo et al. 31 (2020)	7.7	4	32	19.5	6.1	32	4.9%	-11.80 [-14.33, -9.27]	
Cui et al. 52 (2022)	10.4	4.9	30	21.9	9.6	30	4.2%	-11.50 [-15.36, -7.64]	
Hirano et al. 16 (2018)	17.6	9.7	27	9.5	2.2	27	4.3%	8.10 [4.35, 11.85]	
Lin et al. 28 (2020)	11.1	4.8	46	19.8	5.4	61	5.2%	-8.70 [-10.64, -6.76]	
Lin et al. 37 (2017)	13.2	5.2	111	22.4	5.2	255	5.4%	-9.20 [-10.36, -8.04]	÷
Ling et al. 20 (2014)	12.6	3.9	10	28.5	5.5	10	4.0%	-15.90 [-20.08, -11.72]	
Møller et al. 15 (2019)	8.4	3.9	26	14.8	5.8	26	4.8%	-6.40 [-9.09, -3.71]	
Shiraishi et al. 17 2017	13.3	5.1	250	23.7	6.9	477	5.5%	-10.40 [-11.28, -9.52]	÷
Wang et al. 29 (2020)	12.5	5	159	21.6	7	320	5.5%	-9.10 [-10.19, -8.01]	÷
Welsh et al. 21 (2011)	11.9	3.1	10	21.2	5	10	4.3%	-9.30 [-12.95, -5.65]	
Xi et al. 35 (2017)	11.6	6.3	132	19.9	8.3	211	5.3%	-8.30 [-9.85, -6.75]	
Zhang et al. 11 (2021)	16.4	8.3	25	20.3	9.3	25	3.7%	-3.90 [-8.79, 0.99]	
Zhang et al. 51 (2022)	3.7	2.5	11	22.1	9.1	11	3.3%	-18.40 [-23.98, -12.82]	
Subtotal (95% CI)			869			1495	60.4%	-8.74 [-10.53, -6.94]	◆
Heterogeneity: Tau <sup>2</sup> = 8.58	B; Chi² =	124.6	7, df =	12 (P <	0.000	001); l²	= 90%		
Test for overall effect: Z =	9.54 (P	< 0.00	001)						
2.1.3 vs. VMAT									
Anakotta et al. 12 (2020)	8.6	3	19	20.3	4.1	19	5.0%	-11.70 [-13.98, -9.42]	
Celik et al. 13 (2020)	4	1.4	20	9.9	1.9	20	5.5%	-5.90 [-6.93, -4.87]	÷
Cui et al. 52 (2022)	10.4	4.9	30	24.9	14.3	30	3.4%	-14.50 [-19.91, -9.09]	
Liu et al. 14 (2019)	8.2	4.1	19	20.8	7.6	16	4.0%	-12.60 [-16.76, -8.44]	
Warren et al. 19 (2016)	13	3.8	21	21.5	4.1	21	5.0%	-8.50 [-10.89, -6.11]	
Zhang et al. 11 (2021)	16.4	8.3	25	17.3	7.8	25	3.9%	-0.90 [-5.36, 3.56]	
Subtotal (95% CI)			134			131	26.8%	-8.86 [-12.02, -5.69]	◆
Heterogeneity: Tau <sup>2</sup> = 12.6	64; Chi² :	= 43.2	0, df =	5 (P < (	0.0000	)1); l² =	88%		
Test for overall effect: Z =	5.48 (P	< 0.00	001)	,					
							400.00/	0 50 5 44 44 7 0 41	
Total (95% CI)			1151			1877	100.0%	-9.52 [-11.11, -7.94]	$\bullet$
Total (95% CI) Heterogeneity: Tau² = 11.6	69: Chi² :	= 269	1151 .34. df :	= 21 (P	< 0.00	1877 0001): F	<sup>2</sup> = 92%	-9.52 [-11.11, -7.94]	
Total (95% CI) Heterogeneity: Tau² = 11.6 Test for overall effect: Z =	69; Chi² : 11.76 (P	= 269 ' < 0.0	1151 .34, df = 0001)	= 21 (P	< 0.00	1877 0001); F	100.0% 2 = 92%	-9.52 [-11.11, -7.94] -	-20 -10 0 10 20

# h) Heart-V<sub>5</sub>

	Pro	oton	Р	hoton			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD Tot	al Mean	SD	Total	Weight	IV, Random, 95% C	IV. Random, 95% Cl
2.2.1 vs. IMRT								
Cui et al. 52 (2022)	46.2 2	23.5 3	0 75.7	32.1	30	11.5%	-29.50 [-43.74, -15.26]	
Shiraishi et al. 17 2017	41 1	14.8 25	0 90.6	13.5	477	29.2%	-49.60 [-51.80, -47.40]	•
Wang et al. 29 (2020)	41.7 1	18.7 15	9 87.1	20.2	320	27.4%	-45.40 [-49.05, -41.75]	• • • • • • • • • • • • • • • • • • •
Subtotal (95% CI)		43	9		827	68.1%	-45.29 [-51.22, -39.37]	◆
Heterogeneity: Tau <sup>2</sup> = 18.6	5; Chi <sup>2</sup> = '	10.44, df	= 2 (P = 0	.005);	l² = 81%	6		
Test for overall effect: Z =	14.98 (P <	0.00001						
2.2.2 vs. VMAT								
Anakotta et al. 12 (2020)	34.4 1	11.2 1	9 90.7	12.5	19	20.8%	-56.30 [-63.85, -48.75]	
Cui et al. 52 (2022)	46.2 2	23.5 3	0 73.5	33.6	30	11.1%	-27.30 [-41.97, -12.63]	
Subtotal (95% Cl)		4	9		49	31.9%	-42.51 [-70.90, -14.13]	
Heterogeneity: Tau <sup>2</sup> = 385.	.07; Chi² =	• <b>1</b> 1.87, di	= 1 (P =	0.0006	5); l² = 9	2%		
Test for overall effect: Z = 2	2.94 (P = (	0.003)						
								•
Total (95% CI)		48	8		876	100.0%	-45.06 [-51.18, -38.94]	<b>●</b>
Heterogeneity: Tau <sup>2</sup> = 32.1	3; Chi <sup>2</sup> = 2	22.65, df	= 4 (P = 0	.0001)	; I² = 82	2%		
Test for overall effect: Z =	14.42 (P <	0.00001						Proton Photon
Test for subaroup difference	es: Chi <sup>2</sup> =	0.04. df	= 1 (P = 0	.85), l <sup>2</sup>	= 0%			FIGURE FIGURE

i) Heart-V<sub>10</sub>

	Р	roton		Photon			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	IV, Random, 95% CI
2.3.1 vs. IMRT									
Cui et al. 52 (2022)	36.3	18.9	30	67.2	30.8	30	18.9%	-30.90 [-43.83, -17.97]	_ <b>_</b>
Shiraishi et al. 17 2017	35.9	14.3	250	78.3	17.5	477	36.7%	-42.40 [-44.77, -40.03]	•
Welsh et al. 21 (2011)	29	6.3	10	79	12.6	10	26.0%	-50.00 [-58.73, -41.27]	
Subtotal (95% CI)			290			517	81.5%	-42.36 [-49.92, -34.79]	◆
Heterogeneity: Tau <sup>2</sup> = 28	3.99; Chi <sup>i</sup>	<sup>2</sup> = 5.9	3, df =	2 (P = 0	0.05); I	² = 66%	, ,		
Test for overall effect: Z	= 10.97 (	(P < 0.	00001)						
2.3.2 vs. AMAT									
Cui et al. 52 (2022)	36.3	18.9	30	64.2	31.7	30	18.5%	-27.90 [-41.11, -14.69]	
Subtotal (95% CI)			30			30	18.5%	-27.90 [-41.11, -14.69]	◆
Heterogeneity: Not appli	cable								
Test for overall effect: Z	= 4.14 (F	P < 0.0	001)						
Total (95% CI)			320			547	100.0%	-39.52 [-47.45, -31.60]	◆
Heterogeneity: Tau <sup>2</sup> = 43	3.12; Chi	<sup>2</sup> = 10.	53, df =	= 3 (P =	0.01);	² = 72	%		
Test for overall effect: Z	= 9.77 (F	o < 0.0	0001)						-100 -50 0 50 100
Test for subaroup differe	nces: Ch	$1i^2 = 3$	47 df=	= 1 (P =	0.06)	$l^2 = 71$	1%		Proton Photon

	Р	roton		Р	hoton			Mean Difference		Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV	, Random, 95% Cl		
2.4.1 vs. 3D-CRT												
Hirano et al. 16 (2018)	38.5	23.9	27	64.1	23	27	9.9%	-25.60 [-38.11, -13.09]		-		
Subtotal (95% CI)			27			27	9.9%	-25.60 [-38.11, -13.09]		-		
Heterogeneity: Not applic	able											
Test for overall effect: Z =	= 4.01 (F	o < 0.0	001)									
2.4.2 vs. IMRT												
Cui et al. 52 (2022)	16.8	8.7	30	49.7	25.3	30	14.5%	-32.90 [-42.47, -23.33]				
Hirano et al. 16 (2018)	38.5	23.9	27	69.3	27	27	8.7%	-30.80 [-44.40, -17.20]				
Shiraishi et al. 17 2017	27.8	11.6	250	50.8	20.7	477	38.1%	-23.00 [-25.35, -20.65]				
Welsh et al. 21 (2011)	22	6.3	10	44	12.6	10	16.3%	-22.00 [-30.73, -13.27]	_	-		
Subtotal (95% CI)			317			544	77.5%	-25.36 [-30.17, -20.55]	•			
Heterogeneity: Tau <sup>2</sup> = 10	.17; Chi	² = 5.0	8, df =	3 (P = 0	).17); F	² = 41%	)					
Test for overall effect: Z =	= 10.33 (	(P < 0.	00001)									
2.4.3 vs. VMAT												
Cui et al. 52 (2022)	16.8	8.7	30	50.9	28.3	30	12.6%	-34.10 [-44.69, -23.51]				
Subtotal (95% CI)			30			30	12.6%	-34.10 [-44.69, -23.51]				
Heterogeneity: Not applic	able											
Test for overall effect: Z =	= 6.31 (F	<b>o</b> < 0.0	0001)									
Total (95% CI)			374			601	100.0%	-26.60 [-31.09, -22.12]	•			
Heterogeneity: Tau <sup>2</sup> = 12	.31; Chi	² = 8.7	2, df =	5 (P = 0	).12); F	² = 43%	,					
Test for overall effect: Z =	= 11.62 (	P < 0.	00001)	-					-50 -25	U 25 Proton Photon	50	
Test for subaroup differer	nces: Ch	ni² = 2.	20. df =	= 2 (P =	0.33).	l² = 9.2	%					

k) Heart-V<sub>30</sub>

	Р	roton		Р	hoton			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	I IV. Random, 95% CI
2.5.1 vs. 3D-CRT									
Hirano et al. 16 (2018)	22	14.5	27	56.2	21.5	27	5.8%	-34.20 [-43.98, -24.42]	
Ling et al. 20 (2014)	20.9	7.1	10	32.7	9.4	10	6.8%	-11.80 [-19.10, -4.50]	
Subtotal (95% CI)			37			37	12.6%	-22.75 [-44.70, -0.81]	
Heterogeneity: Tau <sup>2</sup> = 231	.49; Chi²	= 12.9	94, df =	1 (P =	0.0003	3); I² = 9	92%		
Test for overall effect: Z =	2.03 (P =	= 0.04)	)						
2.5.2 vs. IMRT									
Bhangoo et al. 31 (2020)	13	5.4	32	21	12.4	32	7.9%	-8.00 [-12.69, -3.31]	
Cui et al. 52 (2022)	10	5.6	30	30.8	16.7	30	7.3%	-20.80 [-27.10, -14.50]	_ <b>-</b>
Hirano et al. 16 (2018)	22	14.5	27	50.7	23.4	27	5.5%	-28.70 [-39.08, -18.32]	
Ling et al. 20 (2014)	20.9	7.1	10	42.3	15.3	10	5.5%	-21.40 [-31.85, -10.95]	
Shiraishi et al. 17 2017	21.5	8.5	250	32.3	17.9	477	8.7%	-10.80 [-12.72, -8.88]	-
Wang et al. 29 (2020)	19.3	8.7	159	27.5	16.7	320	8.7%	-8.20 [-10.48, -5.92]	-
Welsh et al. 21 (2011)	17	6.3	10	25	9.5	10	6.9%	-8.00 [-15.07, -0.93]	
Xi et al. 35 (2017)	18.9	11.6	132	24.4	14.7	211	8.5%	-5.50 [-8.30, -2.70]	-
Zhang et al. 51 (2022)	5	3.8	11	26.8	11.8	11	6.8%	-21.80 [-29.13, -14.47]	
Subtotal (95% CI)			661			1128	65.8%	-13.07 [-16.67, -9.48]	$\bullet$
Heterogeneity: Tau <sup>2</sup> = 21.4	41; Chi² =	= 52.24	4, df = 8	3 (P < 0	.00001	l); l² = 8	35%		
Test for overall effect: Z =	7.13 (P <	< 0.000	001)						
2.5.3 vs. VMAT									
Celik et al. 13 (2020)	4.9	2.3	20	5.9	2.9	20	8.8%	-1.00 [-2.62, 0.62]	1
Cui et al. 52 (2022)	10	5.6	30	38.3	28.8	30	5.5%	-28.30 [-38.80, -17.80]	
Liu et al. 14 (2019)	12.3	7.1	19	18.2	10.2	16	7.4%	-5.90 [-11.83, 0.03]	
Subtotal (95% CI)			69			66	21.6%	-10.51 [-22.16, 1.14]	
Heterogeneity: Tau <sup>2</sup> = 94.4	45; Chi² =	= 27.22	2, df = 2	2 (P < 0	.00001	l); l² = 9	3%		
Test for overall effect: Z =	1.77 (P =	= 0.08)	)						
Total (95% CI)			767			1231	100.0%	-13.89 [-17.84, -9.95]	◆
Heterogeneity: Tau <sup>2</sup> = 45.4	41; Chi² =	= 175.0	07, df =	13 (P <	: 0.000	001); l²	= 93%		
Test for overall effect: Z =	6.91 (P <	< 0.000	001)						-50 -25 U 25 50 Proton Photon
Tool for a barrier state	<u> </u>				001 10				FIOLOII FIOLOII

Test for subaroup differences: Chi<sup>2</sup> = 0.93. df = 2 (P = 0.63). I<sup>2</sup> = 0%

### l) Heart- $V_{40}$

	Р	roton		Р	hoton			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
2.6.1 vs. 3D-CRT									
Hirano et al. 16 (2018)	16.3	11.4	27	48.2	21	27	5.6%	-31.90 [-40.91, -22.89]	
Ling et al. 20 (2014)	16.2	6.4	10	25.8	8.8	10	6.9%	-9.60 [-16.34, -2.86]	
Subtotal (95% CI)			37			37	12.5%	-20.54 [-42.39, 1.31]	
Heterogeneity: Tau <sup>2</sup> = 23	32.15; Cł	ni² = 18	5.08, df	= 1 (P =	= 0.00	01); I² =	= 93%		
Test for overall effect: Z	= 1.84 (F	<b>P</b> = 0.0	7)						
2.6.2 vs. IMRT									
Cui et al. 52 (2022)	6.9	4.2	30	16.8	9.6	30	8.8%	-9.90 [-13.65, -6.15]	
Hirano et al. 16 (2018)	16.3	11.4	27	26.6	16.9	27	6.4%	-10.30 [-17.99, -2.61]	
Ling et al. 20 (2014)	16.2	6.4	10	25.5	11	10	6.2%	-9.30 [-17.19, -1.41]	
Møller et al. 15 (2019)	8.7	5	26	8.9	5.3	26	9.3%	-0.20 [-3.00, 2.60]	+
Shiraishi et al. 17 2017	16.1	7	250	19.6	11.8	477	9.8%	-3.50 [-4.87, -2.13]	-
Welsh et al. 21 (2011)	13	3.2	10	15	6.3	10	8.4%	-2.00 [-6.38, 2.38]	-+
Xi et al. 35 (2017)	14	9.5	132	14.3	9.6	211	9.6%	-0.30 [-2.37, 1.77]	+
Zhang et al. 22 (2008)	30.3	10.9	15	35.9	11.1	15	6.2%	-5.60 [-13.47, 2.27]	
Zhang et al. 51 (2022)	24	20	11	15 4	7 2	11	0 20/	12 00 [ 16 57 7 42]	I



	Pi	roton	1	Photon				Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl		
2.7.1 vs. 3D-CRT											
Ling et al. 20 (2014)	2.8	2.3	10	20	12.6	10	21.2%	-17.20 [-25.14, -9.26]			
Subtotal (95% CI)			10			10	21.2%	-17.20 [-25.14, -9.26]			
Heterogeneity: Not appli	icable										
Test for overall effect: Z	= 4.25 (	P < 0	.0001)								
2.7.2 vs. IMRT											
Ling et al. 20 (2014)	2.8	2.3	10	12	8.6	10	24.7%	-9.20 [-14.72, -3.68]			
Welsh et al. 21 (2011)	8	3.2	10	8	3.2	10	27.9%	0.00 [-2.80, 2.80]			
Zhang et al. 22 (2008)	17.9	6.7	15	15.5	5.2	15	26.3%	2.40 [-1.89, 6.69]			
Subtotal (95% CI)			35			35	78.8%	-1.92 [-7.57, 3.74]			
Heterogeneity: Tau <sup>2</sup> = 20	0.28; Ch	i² = 1	1.35, d	f = 2 (P	= 0.00	); l² =	82%				
Test for overall effect: Z	= 0.66 (	P = 0	.51)								
Total (95% CI)			45			45	100.0%	-5.28 [-12.27, 1.70]			
Heterogeneity: Tau <sup>2</sup> = 43	3.50; Ch	i² = 2	6.61, d	f = 3 (P	< 0.00	001); ľ	² = 89%				
Test for overall effect: Z	Test for overall effect: Z = 1.48 (P = 0.14)								-20 -10 0 10 20		
Test for subaroup differe	ences: C	hi² =	9.44. d	f = 1 (P	= 0.00	2). I² =	89.4%		FIGURE PROLOT		

n) Left ventricle (LV)-D<sub>mean</sub>

	P	roton	1	PI	notor	ı		Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
3.1.1 vs. 3D-CRT											
Ling et al. 20 (2014)	13.9	6.6	10	27.3	5.6	10	20.1%	-13.40 [-18.76, -8.04]			
Subtotal (95% CI)			10			10	20.1%	-13.40 [-18.76, -8.04]			
Heterogeneity: Not appli	cable										
Test for overall effect: Z	= 4.90 (F	<b>P</b> < 0.	00001)								
3.1.2 vs. IMRT											
Ling et al. 20 (2014)	13.9	6.6	10	30.3	5.6	10	20.1%	-16.40 [-21.76, -11.04]	← ∎		
Shiraishi et al. 17 2017	12.7	6.8	250	22.2	7.8	477	29.8%	-9.50 [-10.60, -8.40]	+		
Subtotal (95% CI)			260			487	49.9%	-12.43 [-19.11, -5.75]			
Heterogeneity: Tau <sup>2</sup> = 19	9.90; Chi	² = 6.	10, df =	= 1 (P =	0.01	); I² = 8	4%				
Test for overall effect: Z	= 3.64 (F	<b>P</b> = 0.	0003)								
3.1.3 vs. VMAT											
Celik et al. 13 (2020)	1.9	1.6	20	6.5	1.6	20	30.0%	-4.60 [-5.59, -3.61]			
Subtotal (95% CI)			20			20	30.0%	-4.60 [-5.59, -3.61]	◆		
Heterogeneity: Not appli	cable										
Test for overall effect: Z	= 9.09 (F	<b>P</b> < 0.	00001)								
Total (95% CI)			290			517	100.0%	-10.20 [-14.32, -6.08]	◆		
Heterogeneity: Tau <sup>2</sup> = 14	1.50; Chi	<sup>2</sup> = 59	9.69, df								
Test for overall effect: Z	= 4.85 (F	<b>P</b> < 0.	00001)			,,			-20 -10 0 10 20		
Test for subaroup differe	nces: Ch	ni² = 1	14.78 c	if = 2 (F	e = 0.0	0006)	<sup>2</sup> = 86.5%		Proton Photon		

o) Left anterior descending artery (LAD)-D<sub>mean</sub>

	Р	roton	1	Pł	notor	n		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV. Random, 95% CI
3.2.1 vs. 3D-CRT									
Ling et al. 20 (2014)	0.4	0.6	10	15.1	8.2	10	22.4%	-14.70 [-19.80, -9.60]	
Subtotal (95% CI)			10			10	22.4%	-14.70 [-19.80, -9.60]	
Heterogeneity: Not applic	able								
Test for overall effect: Z =	= 5.65 (F	<b>P</b> < 0.	00001)						
3.2.2 vs. IMRT									
Ling et al. 20 (2014)	0.4	0.6	10	17.6	5.8	10	24.4%	-17.20 [-20.81, -13.59]	_ <b>_</b>
Shiraishi et al. 17 2017	1.6	3.1	250	12.7	7.4	477	26.5%	-11.10 [-11.87, -10.33]	•
Subtotal (95% CI)			260			487	50.9%	-13.88 [-19.84, -7.93]	
Heterogeneity: Tau <sup>2</sup> = 16	.83; Chi	<sup>2</sup> = 10	).47, df	= 1 (P =	= 0.0	01); l² =	90%		
Test for overall effect: Z =	= 4.57 (F	<b>P</b> < 0.	00001)						
3.2.3 vs. VMAT									
Celik et al. 13 (2020)	0.1	0.2	20	3.1	0.5	20	26.6%	-3.00 [-3.24, -2.76]	
Subtotal (95% CI)			20			20	26.6%	-3.00 [-3.24, -2.76]	•
Heterogeneity: Not applic	able								
Test for overall effect: Z =	= 24.91	(P < (	0.00001	1)					
Total (95% CI)			290			517	100.0%	-11.24 [-17.31, -5.16]	
Heterogeneity: Tau <sup>2</sup> = 36	.06; Chi	<sup>2</sup> = 46	62.23, c	lf = 3 (P	, < 0.0	00001);	<sup>2</sup> = 99%		
Test for overall effect: Z =	= 3.62 (F	<b>P</b> = 0.	0003)	,		,.			-20 -10 0 10 20
Test for subaroup differer	nces: Cł	ni² = 3	32.96. c	lf = 2 (P	o < 0.0	00001).	l² = 93.9	%	FICION PHOLON

# p) BM-D<sub>mean</sub>

	Pr	oton		Pł	notor	1		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
5.1.2 vs. IMRT									
Zhang et al. 11 (2021)	11.2	5.5	25	13.8	4.5	25	31.9%	-2.60 [-5.39, 0.19]	
Subtotal (95% CI)			25			25	31.9%	-2.60 [-5.39, 0.19]	



q) BM-V<sub>10</sub>

	Pro	ton	Р	hoton			Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl			
5.2.1 vs. 3D-CRT											
Sumiya et al. 27 (2021)	49 1	0.4 54	57.6	12.6	15	29.7%	-8.60 [-15.55, -1.65]				
Subtotal (95% CI)		54			15	29.7%	-8.60 [-15.55, -1.65]				
Heterogeneity: Not applic	able										
Test for overall effect: Z =	: 2.42 (P =	0.02)									
5.2.2 vs. IMRT											
Zhang et al. 11 (2021)	31.1 1	7.1 25	40.8	17.5	25	15.6%	-9.70 [-19.29, -0.11]				
Subtotal (95% CI)		25			25	15.6%	-9.70 [-19.29, -0.11]				
Heterogeneity: Not applic	able										
Test for overall effect: Z =	: 1.98 (P =	0.05)									
523ve VMAT											
Marron at al. 19 (2017)	12 1	0.2 21	55 7	0.0	21	20 00/	12 70 [ 19 79 6 62]	<b></b>			
Zhang et al. 10 (2017)	31 1 1	7.1 25	38.7	9.9 17.2	21	15 0%	-12.70 [-10.76, -0.02]				
Subtotal (95% CI)	51.1 1	46	30.7	17.2	46	54 7%	-11 22 [-16 34 -6 10]				
Heterogeneity: $Tau^2 = 0.0$	$(0) Chi^2 = 0$	78 df = 1	(P = 0.3)	88)· 12 =	: 0%	04.170	-11.22 [-10.04, -0.10]				
Test for overall effect: 7 =	: 4 29 (P <	0.0001	(1 – 0.0	, i -	0 /0						
	4.20 (1	0.0001)									
Total (95% CI)		125			86	100.0%	-10.21 [-13.99, -6.42]	◆			
Heterogeneity: Tau <sup>2</sup> = 0.0	0; Chi² = 1	1.15, df = 3	(P = 0.7)	76); l² =	0%						
Test for overall effect: Z =	5.28 (P <	0.00001)	-					-20 -10 0 10 20			
Test for subaroup differer	ices: Chi <sup>2</sup> :	= 0.37. df =	= 2 (P =	0.83).	² = 0%						

# r) BM-V<sub>20</sub>

	Р	roton		Р	hoton			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	I IV, Random, 95% CI
5.3.1 vs. 3D-CRT									
Sumiya et al. 27 (2021)	34.3	8.7	54	50.8	12.7	15	24.4%	-16.50 [-23.33, -9.67]	
Subtotal (95% CI)			54			15	24.4%	-16.50 [-23.33, -9.67]	
Heterogeneity: Not applica	able								
Test for overall effect: Z =	4.73 (P	< 0.00	0001)						
5.3.2 vs. IMRT									
Zhang et al. 11 (2021)	22.8	12.3	25	28.3	11.5	25	24.9%	-5.50 [-12.10, 1.10]	
Subtotal (95% CI)			25			25	24.9%	-5.50 [-12.10, 1.10]	
Heterogeneity: Not applica	able								
Test for overall effect: Z =	1.63 (P	= 0.10	0)						
5.3.3 vs. VMAT									
Warren et al. 18 (2017)	34.7	10.8	21	49.1	8.6	21	26.6%	-14.40 [-20.30, -8.50]	<b>_</b>
Zhang et al. 11 (2021)	22.8	12.3	25	27.4	12.8	25	24.1%	-4.60 [-11.56, 2.36]	
Subtotal (95% CI)			46			46	50.7%	-9.68 [-19.28, -0.08]	
Heterogeneity: Tau <sup>2</sup> = 37.	18; Chi²	= 4.43	3, df = <sup>-</sup>	1 (P = 0	.04); l²	e = 77%			
Test for overall effect: Z =	1.98 (P	= 0.05	5)		,.				
Total (95% CI)			125			86	100.0%	-10 33 [-16 20 -4 47]	
Hotorogonoity: $T_{2}u^2 = 24$	61 · Chi2	- 0.60		2 ( - 0	001-12	- 60%	100.070	-10.00 [-10.20, -4.47]	
Test for everall effect: Z =		- 9.00	0, ur = .	5 (F = 0	.02); 1	- 09%			-20 -10 0 10 20
Test for overall effect: $Z =$	3.45 (P	= 0.00	100) 10 46 -	а (п —	0.07	12 - 64	E0/		Proton Photon
lest for subdroub differen	ces: Ch	r = 5.1	19. df =	Z (P =	U.U/).	r = 61.	0%0		

# s) SC-D<sub>max</sub>

	P	roton		P	hotor	n		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
4.1.1 vs. 3D-CRT									
Hirano et al. 16 (2018)	38.1	5	27	47.3	2.2	27	7.7%	-9.20 [-11.26, -7.14]	-
Ling et al. 20 (2014)	11.6	10	10	31.2	9.7	10	4.6%	-19.60 [-28.23, -10.97]	
Subtotal (95% CI)			37			37	12.3%	-13.52 [-23.56, -3.48]	
Heterogeneity: Tau <sup>2</sup> = 43.8	82; Chi² =	= 5.27,	df = 1	(P = 0.0)	02); ľ	² = 81%			
Test for overall effect: Z =	2.64 (P =	= 0.008	3)						
4.1.2 vs. IMRT									
Cui et al. 52 (2022)	40.2	3	30	45	3.3	30	7.9%	-4.80 [-6.40, -3.20]	<b>-</b>
Hirano et al. 16 (2018)	38.1	5	27	39.7	2.6	27	7.7%	-1.60 [-3.73, 0.53]	-
Lin et al. 28 (2020)	38.3	4.5	46	37.1	8	61	7.6%	1.20 [-1.19, 3.59]	+-
Ling et al. 20 (2014)	11.6	10	10	36.9	3.5	10	5.6%	-25.30 [-31.87, -18.73]	
Mu et al. 23 (2011)	34.9	5	10	41.4	1	10	7.3%	-6.50 [-9.66, -3.34]	-
Welsh et al. 21 (2011)	36.8	11.8	10	36.7	9.5	10	4.2%	0.10 [-9.29, 9.49]	
Zhang et al. 11 (2021)	31.9	13	25	37.6	6.5	25	6.1%	-5.70 [-11.40, -0.00]	
Zhang et al. 22 (2008)	25.4	8.4	15	40.6	1.9	15	6.8%	-15.20 [-19.56, -10.84]	
Zhang et al. 51 (2022)	37.6	7.3	11	46.4	3.6	11	6.5%	-8.80 [-13.61, -3.99]	
Subtotal (95% CI)			184			199	59.7%	-7.14 [-10.95, -3.34]	•
Heterogeneity: Tau <sup>2</sup> = 28.3	36; Chi² =	96.46	6, df = 8	3 (P < 0	.0000	01); I <sup>2</sup> =	92%		
Test for overall effect: Z =	3.68 (P =	= 0.000	02)						
4.1.3 vs. VMAT									
Anakotta et al. 12 (2020)	30.6	6	19	36.8	5.5	19	7.1%	-6.20 [-9.86, -2.54]	
Cui et al. 52 (2022)	40.2	3	30	49.1	6.8	30	7.5%	-8.90 [-11.56, -6.24]	-
Liu et al. 14 (2019)	38.4	3.6	19	36.1	5.8	16	7.3%	2.30 [-0.97, 5.57]	
Zhang et al. 11 (2021)	31.9	13	25	34.2	6.1	25	6.1%	-2.30 [-7.93, 3.33]	-
Subtotal (95% CI)			93			90	28.0%	-3.86 [-9.39, 1.67]	➡
Heterogeneity: Tau <sup>2</sup> = 27.9	95; Chi² =	= 28.51	1, df = 3	3 (P < 0	.0000	01); I <sup>2</sup> =	89%		
Test for overall effect: Z =	1.37 (P =	= 0.17)							





eFigure 3. Pooled Analysis of pCR (Proton vs Photon Therapy)

	Proton the	erapy	Photon th	erapy		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Bhangoo et al. <sup>31</sup> 2020	5	15	7	18	20.2%	0.79 [0.19, 3.29]	
Choi et al. <sup>49</sup> 2022	4	14	5	14	17.0%	0.72 [0.15, 3.54]	
DeCesaris et al. <sup>30</sup> 2020	3	18	8	36	21.2%	0.70 [0.16, 3.04]	
Lin et al. <sup>28</sup> 2020	14	21	18	30	23.6%	1.33 [0.42, 4.27]	
Macomber et al <sup>34</sup> 2018	3	16	8	39	18.0%	0 89 [0 20 3 91]	



### a) G2+ RE

	Proton th	erapy	Photon th	erapy		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	1	M-H, Fixed, 95% Cl
1.1.1 Acute								
Bhangoo et al. 31 (2020)	13	32	8	32	9.5%	2.05 [0.71, 5.96]		
DeCesaris et al. 30 2020	6	18	10	36	8.9%	1.30 [0.38, 4.41]		
Subtotal (95% CI)		50		68	18.4%	1.69 [0.76, 3.75]		
Total events	19		18					
Heterogeneity: Chi <sup>2</sup> = 0.30	), df = 1 (P =	0.58); l²	= 0%					
Test for overall effect: Z =	1.29 (P = 0.2	20)						
1.1.2 Unknown								
Xi et al. 35 (2017)	60	132	97	211	81.6%	0.98 [0.63, 1.52]		
Subtotal (95% Cl)		132		211	81.6%	0.98 [0.63, 1.52]		<b>•</b>
Total events	60		97					
Heterogeneity: Not applica	able							
Test for overall effect: Z =	0.09 (P = 0.9	93)						
Total (95% CI)		182		279	100.0%	1.11 [0.76, 1.63]		<b>•</b>
Total events	79		115					
Heterogeneity: Chi <sup>2</sup> = 1.66	δ, df = 2 (P =		+					
Test for overall effect: Z =	0.54 (P = 0.5		0.05	U.2 1 5 20 Broton thorapy Bhoton thorapy				
Test for subaroup differen	ces: Chi <sup>2</sup> = 1			Froton therapy Froton therapy				

b) G2+ RP

	Proton the	erapy	Photon the	erapy		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
1.2.1 Acute							
Lin et al. 28 (2020)	1	46	3	61	14.1%	0.43 [0.04, 4.27]	
Subtotal (95% CI)		46		61	14.1%	0.43 [0.04, 4.27]	
Total events	. 1		3				
Heterogeneity: Not applicab		-					
Test for overall effect: $Z = 0$	.72 (P = 0.4	()					
1.2.2 Late							
Makishima et al. 38 2015	0	25	4	19	27.9%	0.07 [0.00, 1.34]	
Sumiya et al. 27 (2021)	0	54	0	15		Not estimable	
Subtotal (95% CI)		79		34	27.9%	0.07 [0.00, 1.34]	
Total events	0		4				
Heterogeneity: Not applicab	le						
Test for overall effect: Z = 1.	.77 (P = 0.0	8)					
1.2.3 Unknown							
Xi et al. 35 (2017)	5	132	14	211	58.0%	0.55 [0.19, 1.58]	
Subtotal (95% CI)		132		211	58.0%	0.55 [0.19, 1.58]	-
Total events	5		14				
Heterogeneity: Not applicab	le						
Test for overall effect: Z = 1.	.11 (P = 0.2	7)					
Total (95% CI)		257		306	100.0%	0.40 [0.17, 0.97]	•
Total events	6		21				
Heterogeneity: Chi <sup>2</sup> = 1.74,	df = 2 (P = 0	).42); l²	= 0%				
Test for overall effect: Z = 2	.03 (P = 0.0	4)					Proton therapy Photon therapy
Test for subaroup difference	es: Chi² = 1.	70. df =	2 (P = 0.43)	$I^2 = 0\%$	•		······································

c) G2+ PE

	Proton the	erapy	Photon th	erapy		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H, Fixed, 95% CI	
1.3.1 Late									
Makishima et al. 38 2015	0	25	2	19	20.2%	0.14 [0.01, 3.04]			
Suh et al. 25 (2021)	3	54	0	15	5.3%	2.11 [0.10, 43.05]			
Subtotal (95% CI)		79		34	25.5%	0.55 [0.10, 2.91]			
Total events	3		2						
Heterogeneity: Chi <sup>2</sup> = 1.53	, df = 1 (P =	0.22); l²	= 35%						
Test for overall effect: Z = 0	0.71 (P = 0.4	8)							
1.3.2 Unknown									
Xi et al. 35 (2017)	7	132	14	211	74.5%	0.79 [0.31, 2.01]			
Subtotal (95% CI)		132		211	74.5%	0.79 [0.31, 2.01]			
Total events	7		14						
Heterogeneity: Not applica	ble								
Test for overall effect: Z = 0	0.50 (P = 0.6	52)							
Total (95% CI)		211		245	100.0%	0.73 [0.32, 1.65]		•	
Total events	10		16						
Heterogeneity: Chi <sup>2</sup> = 1.62	, df = 2 (P =	0.44); l²	= 0%				+		
Test for overall effect: Z = 0	0.76 (P = 0.4	-5)					0.002	U.1 1 1U Broton thorony Bhoton thorony	500
Test for subaroup difference	es: Chi <sup>2</sup> = 0.	14. df =	1 (P = 0.71)	). $I^2 = 0\%$	,			Proton therapy Photon therapy	

#### d) G2+ PCE

	Proton therapy	Photon therapy	Odds Ratio	Odds Ratio
Study or Subgroup	Events Tota	I Events Total We	eight M-H, Random, 95% Cl	M-H, Random, 95% Cl
4.4.4.1.=4=			•	



# e) G3+ RE

	Proton the	erapy	Photon th	erapy		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H, Fixed, 95% Cl
2.1.1 Acute					-			
Bhangoo et al. 31 (2020)	1	32	0	32	1.7%	3.10 [0.12, 78.87]		
Lin et al. 28 (2020)	6	46	8	61	21.7%	0.99 [0.32, 3.09]		
Subtotal (95% CI)		78		93	23.4%	1.15 [0.40, 3.29]		$\rightarrow$
Total events	7		8					
Heterogeneity: Chi <sup>2</sup> = 0.42, c	df = 1 (P = )	0.52); l²	= 0%					
Test for overall effect: Z = 0.2	26 (P = 0.8	0)						
2.1.2 Unknown								
Xi et al. 35 (2017)	15	132	31	211	76.6%	0.74 [0.39, 1.44]		
Subtotal (95% CI)		132		211	76.6%	0.74 [0.39, 1.44]		
Total events	15		31					
Heterogeneity: Not applicabl	е							
Test for overall effect: Z = 0.8	88 (P = 0.3	8)						
Total (95% CI)		210		304	100.0%	0.84 [0.48, 1.46]		•
Total events	22		39					
Heterogeneity: Chi <sup>2</sup> = 0.84, c	df = 2 (P = )	0.66); l²	= 0%				+	
Test for overall effect: $Z = 0.0$	62 (P = 0.5	4)					0.01	U.1 1 10 100
Test for subaroup differences	s: Chi <sup>2</sup> = 0.	, 47. df =	1 (P = 0.49	). $I^2 = 0\%$	<b>,</b>			Proton therapy Photon therapy

f) G3+ RP

	Proton the	erapy	Photon the	erapy		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% Cl
2.2.1 Acute							
Lin et al. 28 (2020)	0	46	1	61	17.1%	0.43 [0.02, 10.89]	
Suh et al. 25 (2021)	0	48	0	29		Not estimable	
Subtotal (95% CI)		94		90	17.1%	0.43 [0.02, 10.89]	
Total events	0		1				
Heterogeneity: Not applica	ble						
Test for overall effect: Z = 0	0.51 (P = 0.6	1)					
2.2.2 Late							
Makishima et al. 38 2015	0	25	1	19	22.2%	0.24 [0.01, 6.28]	
Sumiya et al. 27 (2021)	0	54	0	15		Not estimable	
Subtotal (95% CI)		79		34	22.2%	0.24 [0.01, 6.28]	
Total events	0		1				
Heterogeneity: Not applica	ble						
Test for overall effect: Z = 0	0.85 (P = 0.3	9)					
2.2.3 Unknown							
Xi et al. 35 (2017)	2	132	6	211	60.7%	0.53 [0.10, 2.64]	
Subtotal (95% CI)		132		211	60.7%	0.53 [0.10, 2.64]	
Total events	2		6				
Heterogeneity: Not applica	ble						
Test for overall effect: Z = 0	0.78 (P = 0.4	4)					
Total (95% CI)		305		335	100.0%	0.45 [0.12, 1.67]	-
Total events	2		8			-	
Heterogeneity: Chi <sup>2</sup> = 0.18	, df = 2 (P = 0	0.92); l²	= 0%				
Test for overall effect: Z =	1.20 (P = 0.2	3)					0.001 0.1 1 10 1000
Test for subaroup difference	es: Chi <sup>2</sup> = 0.	18. df =	2(P = 0.92)	. I² = 0%	)		Proton therapy Photon therapy

g) G3+ PE

	Proton the	erapy	Photon th	erapy		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
2.3.1 Acute							
Lin et al. 28 (2020)	0	46	3	61	38.8%	0.18 [0.01, 3.57]	
Suh et al. 25 (2021)	0	48	0	29		Not estimable	
Subtotal (95% CI)		94		90	38.8%	0.18 [0.01, 3.57]	
Total events	0		3				
Heterogeneity: Not applicab	ole						
Test for overall effect: Z = 1	.13 (P = 0.2	6)					
	,	,					
2.3.2 Late							
Makishima et al. 38 2015	0	25	1	19	21.6%	0.24 [0.01, 6.28]	
Sumiya et al. 27 (2021)	0	54	0	15		Not estimable	
Subtotal (95% Cl)		79		34	21.6%	0.24 [0.01, 6.28]	
Total events	0		1				
Heterogeneity: Not applicab	ole						
Test for overall effect: Z = 0	.85 (P = 0.3	9)					
	,	,					
2.3.3 Unknown							
Xi et al. 35 (2017)	1	132	4	211	39.7%	0.40 [0.04, 3.57]	
Subtotal (95% Cl)		132		211	39.7%	0.40 [0.04, 3.57]	
Total events	1		4				
Heterogeneity: Not applicab	ole						
Test for overall effect: Z = 0	.83 (P = 0.4	1)					
	,	,					
Total (95% CI)		305		335	100.0%	0.28 [0.06, 1.32]	
Total events	1		8				

Heterogeneity: Chi<sup>2</sup> = 0.19, df = 2 (P = 0.91); l<sup>2</sup> = 0% Test for overall effect: Z = 1.61 (P = 0.11) Test for subaroup differences: Chi<sup>2</sup> = 0.19, df = 2 (P = 0.91), l<sup>2</sup> = 0%



# h) G3+ PCE

	Proton th	erapy	Photon th	erapy		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H, Fixed, 95% Cl	
2.4.1 Acute									
Lin et al. 28 (2020)	0	46	1	61	25.1%	0.43 [0.02, 10.89]	-		
Suh et al. 25 (2021)	0	48	0	29		Not estimable			
Subtotal (95% CI)		94		90	25.1%	0.43 [0.02, 10.89]	-		
Total events	0		1						
Heterogeneity: Not applicabl	le								
Test for overall effect: Z = 0.	51 (P = 0.6	51)							
2.4.2 Late									
Makishima et al. 38 2015	0	25	0	19		Not estimable			
Sumiya et al. 27 (2021)	0	54	0	15		Not estimable			
Subtotal (95% CI)	,	79		34		Not estimable			
Total events	0		0						
Heterogeneity: Not applicabl	е								
Test for overall effect: Not ap	pplicable								
2.4.3 Unknown									
Xi et al. 35 (2017)	1	132	5	211	74.9%	0.31 [0.04, 2.72]			
Subtotal (95% CI)		132		211	74.9%	0.31 [0.04, 2.72]			
Total events	1		5						
Heterogeneity: Not applicabl	e								
Test for overall effect: Z = 1.	05 (P = 0.2	9)							
		205		225	100.0%	0.24 [0.06.2.06]			
		305	0	335	100.0%	0.34 [0.06, 2.06]			
	1	0.07) 12	6				L		
Heterogeneity: $Chi^2 = 0.03$ , o	at = 1 (P =	0.87); l²	= 0%				0.001	0.1 1 10	1000
Test for overall effect: $Z = 1$ .	17 (P = 0.2)	:4)					Pro	oton therapy Photon therapy	

Test for subaroup differences: Chi<sup>2</sup> = 0.03. df = 1 (P = 0.87). I<sup>2</sup> = 0%

# i) G4+ lymphocytopenia

	Proton the	erapy	Photon th	erapy		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
3.1.1 Acute							
Bhangoo et al. 31 (2020)	6	32	9	32	2.9%	0.59 [0.18, 1.91]	
Choi et al. 49 (2022)	2	15	3	16	1.0%	0.67 [0.10, 4.67]	· · · · · · · · · · · · · · · · · · ·
Fang et al. 36 (2018)	34	110	52	110	14.2%	0.50 [0.29, 0.87]	
Lin et al. 28 (2020)	12	46	32	61	8.0%	0.32 [0.14, 0.73]	
Routman et al. 32 (2019)	12	50	30	50	9.0%	0.21 [0.09, 0.50]	
Shiraishi et al. 33 2018	24	136	55	136	17.9%	0.32 [0.18, 0.55]	<b>_</b>
Zhu et al. 46 (2021)	54	246	231	500	47.0%	0.33 [0.23, 0.46]	
Subtotal (95% CI)		635		905	100.0%	0.35 [0.28, 0.44]	◆
Total events	144		412				
Heterogeneity: Chi <sup>2</sup> = 4.42,	df = 6 (P = 1	0.62); I²	= 0%				
Test for overall effect: Z = 8	.90 (P < 0.0	0001)					
Total (95% CI)		635		905	100.0%	0.35 [0.28, 0.44]	◆
Total events	144		412				
Heterogeneity: Chi <sup>2</sup> = 4.42,	df = 6 (P = 1	0.62); I²	= 0%				
Test for overall effect: Z = 8	.90 (P < 0.0	0001)					0.1 0.2 0.5 1 2 5 10 Proton therapy Photon therapy
Test for subaroup difference	es: Not appl	icable					Froton merapy Photon merapy

### eFigure 5. Example of Single-Rate Pooled Analysis of OS and PFS for Proton Therapy

A/B: 2y-OS; C/D: 2y-PFS; A/C: sub-group by treatment modalities (neoadjuvant, racial, or mixed); B/D: sub-group by stage (III-IV < 50% or  $\geq$  50%).



### eFigure 6. Single-Rate Pooled Analysis of CR (Proton Therapy)







Ribeiro et al <sup>10</sup>	10 (20)	PBT (IMPT) ve VMAT (4DCT)	_	Lung: *Dman   · 3 8Gy	No SS change
2021	10 (20)	$\mathbf{D} \mathbf{T} (\mathbf{H} \mathbf{H} \mathbf{T} \mathbf{I})  \forall \mathbf{N} \mathbf{I} \mathbf{A} \mathbf{I} (4 \mathbf{D} \mathbf{C} \mathbf{I})$ $\mathbf{D} \mathbf{T} \mathbf{V} \cdot \mathbf{A} \mathbf{I} \mathbf{A} \mathbf{C} \mathbf{v} / 2 \mathbf{E}$	-	Heart: *D	no so change
2021		$F = 1 V \cdot 41.4 U Y/23F$ Site: L (2004)		neait. "D <sub>mean↓</sub> : 9.309.	
Zhang et al <sup>11</sup>	25	PRT (PSPT) vs IMPT/ VMAT	Lung: D	# (vs. IMRT) Lung. *D_mail. 3 (Gv. *Vs. 10). 25 30/ 12 00/ Val.	No SS change
2021	25	(ADCT)	$V_{aa} = 2000,  V_{aa} = 2000,  V_{aaa} = 2000,  V_{aaa} = 2000,  V_{aaaa} = 2000,  $	(vs. hviki) Lung. Dmeant. 5.00y, $v_{5}$ , $101$ , 25.570, 12.570, $v_{201}$ .	No 55 change
2021		(4DC1)	$V_{20} < 2070$ ,	$V_{\rm P} * D_{\rm mean} = 1.40 {\rm Gy} * V_{10} {\rm cm} + 12.5\% {\rm max} = 2.40 {\rm Gy}$	
		PTV: 50.4 Gy/28F	Heart: $D_{\text{mean}} < 2000 \text{ y};$	<b>V D.</b> "Dmean]: 4.9Gy, *V 10, 201: 18.576, 12.076. # (via VMAT) Lung: *D = 1: 2.6Gy, *V = $x = 12.21.79(-20.49(-2.79))$	
		Site: -	<b>vB:</b> $D_{\text{mean}} < 18.8 \text{Gy}, v_{10} < 34.2\% (< 200)$	* (VS. VIMAI) Lung: * $D_{mean}\downarrow$ : 3.0Gy, *V5, 10, 20 $\downarrow$ : 31.7%, 20.4%, 3.7%.	
			cc), $v_{20} < 44.3\%$ (<225 cc).	Heart: $D_{mean}\downarrow$ : 2.6Gy. SC: $D_{max}\uparrow$ : 4.1Gy.	
12				VB: $*D_{\text{mean}}$ : 2.8Gy, $*V_{10,20}$ : 14.9%, 8.2%.	
Anakotta et al. <sup>12</sup>	19 (20)	PBT (IMPT) vs. VMAT (4DCT)	Lung: $D_{mean} \leq 20$ Gy, $V_5 \leq 70\%$ , $V_{20} \leq$	Lung: $D_{\text{mean}}$ : 5.0Gy, $V_{5,20}$ : 32.6%, 5.6%.	No SS change
2020		PTV: 41.4-51Gy/17-28F	30%;	Heart: $D_{\text{mean}}\downarrow$ : 11.8Gy, $V_5\downarrow$ : 56.3%.	
		Site: L (18)	Heart: D <sub>mean</sub> ≤26Gy.	SC: $D_{max}\downarrow$ : 6.2Gy.	
Celik et al. <sup>13</sup>	20	PBT (IMPT) vs. VMAT	Lung: $D_{mean} \leq 12$ Gy, $V_{20} \leq 20\%$ ;	Lung: $D_{\text{mean}}\downarrow$ : 5.7Gy, $V_{20}\downarrow$ : 4.6%.	SS HI ↓; no SS
2020		PTV: 41.4Gy/23F	Heart: $D_{mean} \leq 10 Gv, V_{30} \leq 10\%$ .	Heart: $D_{\text{mean}} \downarrow$ : 6.2Gy, $V_{30} \downarrow$ : 1.0%.	CI
		Site: L		LV/ LCA/ LAD: *Dmean J: 4.6/ 3.3/ 3.0Gy.	
Liu et al. <sup>14</sup>	19 vs. 16	PBT (IMPT) vs. VMAT (4DCT)	Lung: D <sub>mean</sub> <15Gy, V <sub>5</sub> <60%, V <sub>20</sub> <15%;	^Lung: *D <sub>mean</sub> ↓: 4.8Gy, *V <sub>5</sub> ↓: 32.5%, V <sub>20</sub> ↓: 1.8%. (med)	No SS change
2019		PTV: 41.4-50.4 Gy	Heart: D <sub>mean</sub> <26Gy, V <sub>25</sub> <50%,	^Heart: $D_{\text{mean}} \downarrow$ : 14.3Gy, $V_{20} \downarrow$ : 35.5%, $V_{30, 40} \downarrow$ : 7.0%, 2.1%.	-
		Site: -	V <sub>40</sub> <30%.	^SC: D <sub>max</sub> ↑: 2.9Gy.	
Møller et al. <sup>15</sup>	26	PBT (SFUD) vs. IMRT	Lung: D <sub>mean</sub> <19Gy, V5<60%, V20<35%;	<sup>#</sup> Lung: $*D_{mean}\downarrow$ : 6.6Gv, $*V_{5,20}\downarrow$ : 41.1%, 8.2%.	No SS change
2019	-	PTV: 41.4-50Gv/23-25F	Heart: $V_{25} < 40\%$ . $V_{40} < 30\%$ .	<sup>#</sup> Heart: * $D_{mean}$ ]: 7.9Gv. V <sub>25</sub> ]: 5.7%. V <sub>40</sub> ↑: 0.2%.	er en
		Site: M/L (5/21)		······ — — — — — — — — — — — — — — — —	
Hirano et al. <sup>16</sup>	27 (37)	PBT vs. IMRT/ 3D-CRT	PBT: Lung: V20<20%: Heart	(vs. IMRT) Lung; *Dmean : 3.6Gv. *V5 10 15 20 : 19 9% 8 7% 5 1%	(vs. IMRT) SS
2018	27 (37)	PTV 60Gv/30F	$D_{max} < 26 Gv V_{20} < 46\%$	6 1% SC: Draw 1: 1 6Gv	CL↑·
2010		Site: $II/M/I$ (5/9/13)	$IMRT \cdot I ung \cdot V_{20} < 30\% \cdot Heart$	Heart: *D_max $\uparrow$ : 8 1Gy *V <sub>20-20-40</sub> ] : 30.8% 28.7% 10.3%	(vs 3D-CRT)
		Site. 0/W/ E (5/)/15)	$D_{\text{max}} = 50 \text{Gy}$	(ve 3D CPT) Lung: $*D_{max}$ : 2 4Gy $*V_{5}$ 201: 78% 53%: Vio vs.	(vs. 5D-CRI)
				(vs. 5D-CR1) Lung. Dmean $\therefore$ 2.4Gy, vs. 20 $\therefore$ 7.670, 5.570, v 10, 15 $\therefore$	55 CI4
			SD-CRI: -	4.4%, 5.6%. SC. $D_{max}$ ; 9.109.	
SI: 11: 4 117	250 477			Heart: " $D_{\text{mean}\downarrow}$ : 13.4Gy, " $V_{20,30,40\downarrow}$ : 25.6%, 34.1%, 31.9%.	N GG I
Shiraishi et al."	250 vs. 477	PB1 (95% PSP1) vs. IMR1	Lung: $D_{\text{mean}} \leq 20$ Gy, $V_5 < 55\%$ , $V_{20} \leq$	Heart: * $D_{\text{mean}}$ : 10.4Gy, * $V_{5, 10, 20, 30, 40}$ : 49.6%, 42.4%, 23.0%,	No SS change
2017		(4DC1)	35%;	10.8%, 3.5%.	
		PTV: 50.4Gy/28F	Heart: $D_{mean} < 26 Gy, V_{30} \le 45\%$ .	LA/ LV: $D_{mean}$ : 4.0/ 9.5Gy; RA/ RV: $D_{mean}$ : 10.0/ 14.8 Gy.	
. 10		Site: L (223 vs. 428)		LMC/ LAD/ LCX/ RCA: *D <sub>mean</sub> ↓: 16.8/ 11.1/ 3.5/ 15.1 Gy.	
Warren et al. <sup>18</sup>	21	PBT vs. VMAT	TV: -	$^{\text{#}}\text{TV: *}\text{D}_{\text{mean}}\downarrow$ : 3.3Gy, *V <sub>10, 20</sub> $\downarrow$ : 4%, 10.8%.	No SS change
2017		PTV: 62.5 Gy/25F			
		Site: M			
Warren et al. <sup>19</sup>	21	PBT vs. VMAT	Lung: D <sub>mean</sub> <20Gy, V <sub>20</sub> <25%;	Lung: $D_{mean}\downarrow: 6.8Gy, *V_{20}\downarrow: 8.8\%.$	No SS change
2016		PTV: 62.5 Gy/25F	Heart: $D_{mean} < 25$ Gy, $V_{30} < 45$ %.	Heart: $D_{\text{mean}}\downarrow$ : 8.5Gy.	
		Site: M			
Ling et al. <sup>20</sup>	10	PBT vs. 3DCRT/IMRT	Lung: V <sub>20</sub> <30%;	(vs. IMRT) Lung: $D_{mean} \downarrow$ : 3.5Gy, $V_{5, 10, 15} \downarrow$ : 25.5%, 18.4%, 10.6%,	(vs. IMRT) no
2014		PTV: 50.4Gy/28F	Heart: V <sub>40</sub> <30%.	$V_{20, 30, 50}\downarrow$ : 0.9%, 0.5%, 0.5%, $V_{40}\uparrow$ : 0.8%.	SS CI, HI
		Site: L		Heart: $D_{mean} \downarrow$ : 15.9Gy, $V_{25, 30, 40, 50} \downarrow$ : 30.4%, 21.4%, 9.3%, 9.2%.	(vs. 3D-CRT)
				LAD/ LV/ PC: *Dmean J: 17.2/ 16.4/ 12.5Gy.	no SS CI, SS HI
				SC: *D <sub>max</sub> ↓: 25.3Gy.	↑
				(vs. 3D-CRT) Lung: $D_{mean}\downarrow$ : 3.4Gy, $V_{5, 50}\downarrow$ : 12.7%, 2.2%; $V_{10, 15, 20}$ ,	
				30, 40↓: 9.7%, 6.6%, 6.8%, 3.7%, 0.4%.	
				SC: *D <sub>max</sub> ↓: 19.6Gy.	
				Heart: *D <sub>mean</sub> ↓: 14.9Gy, *V <sub>25, 30, 40, 50</sub> ↓: 32.6%, 11.8%, 9.6%, 17.2%.	
				LAD/ LV/ PC: *D <sub>mean</sub> J: 14.7/ 13.9/ 11.3Gy.	
Welsh et al. <sup>21</sup>	10	PBT (IMPT) vs. IMRT (4DCT)	-	Lung: $D_{\text{mean}}$ : 3.4Gy, $V_{5,10}$ : 19%, 8%, $V_{20}$ : 3%.	-
2011	-	PTV: 50.4Gv/28F		Heart: $*D_{mean}$ : 9.3Gv. $*V_{10.20,30}$ : 50%, 22%, 8%, $V_{40.50}$ : 2%, 0%	
		Site: -		SC Draw + 0.1Gv	
<b>Zhang et al</b> $^{22}$	15	PRT (PSPT) ve IMRT (ADCT)		#Lung: *D_max $ \cdot  3.0 \text{Gv}$ *Vs to 20 20 $ \cdot  17.40\%$ 8.40% 5.00% 0.50%	SS CI ↑
2008	15	$PTV \cdot 50 \ 4 \ G_{V} / 25E$	-	$= 1000 \text{ Jm}(3.000 \text{ Jm})^{-1.00} \text{ Jm})^{-1.00} \text{ Jm}(3.000 \text{ Jm})^{-1.00} \text{ Jm}(3.000 \text{ Jm})^{-1.00} \text{ Jm}(3.000 \text{ Jm})^{-1.00} \text{ Jm})^{-1.00} \text{ Jm}(3.000 \text{ Jm})^{-1.00} \text{ Jm}(3.000 \text{ Jm})^{-1.00} \text{ Jm})^{-1.00} \text{ Jm}(3.000 \text{ Jm})^{-1.00} \text{ Jm})^{-1.00} \text{ Jm}(3.000 \text{ Jm})^{-1.00} \text{ Jm})^{-1.00} \text{ Jm})^{-1.00} \text{ Jm}(3.000 \text{ Jm})^{-1.00} \text{ Jm}$	55 CI
2000		1 I V. JU.4 UY/2JF Site: I		#LLoopt: *XL	
		SHEL		$\mathbf{nearr}_{\mathbf{v}}$ , $\mathbf{v}$ 401; $\mathbf{o}$ , $\mathbf{v}$ 70; $\mathbf{v}$ 501; $\mathbf{v}$ , $\mathbf{v}$ %.	

eTable 1. Detailed Comparison Informat	ion on OARs Dosimetric and Planning	Quality From Proton and Photon	Radiotherapy Planning
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Mu et al. <sup>23</sup>	10	PBT vs. IMRT	Lung: $V_5 < 42\%$ , $V_{10} < 35\%$ ; $V_{20} < 20\%$ ;	Lung: $D_{mean}\downarrow$ : 4.8Gy, $V_{5, 20}\downarrow$ : 31.4%, 6.1%.	SS CI ↑	
2011		PTV: 60Gy/30F		SC: $D_{max}\downarrow$ : 6.5Gy.		
		Site: U				
Wang et al. <sup>24</sup>	55	PBT (PSPT) vs. IMRT	Lung: $D_{mean} \leq 20$ Gy, $V_{20} \leq 35\%/30\%$ ;	Lung: *D <sub>mean</sub> ↓: 2.9Gy, *V <sub>5, 10, 20</sub> ↓: 20.3%, 9.7%, 4.2%.	No SS cha	ange
2015		PTV: 50.4Gy/28F	Heart: $D_{mean} < 26Gy, V_{30} \le 45\%$ .	Heart: *V <sub>10, 20, 30</sub> ↓: 32.7%, 13.3%, 2.5%.		
		Site: -		SC: $D_{max}\downarrow$ : 8.5Gy.		
Suh et al. <sup>25</sup>	48 vs. 29	PBT vs. 3D-CRT/IMRT (24/5)	-	$^{\#}$ ^(vs. photon) Lung: *D_mean↓: 4.8Gy, *V_5, $_{10,\ 20,\ 30}\downarrow$ : 26.1%, 14.6%,	-	
2021		PTV: 66Gy/33F (med)		3.5%.		
		*Site: L (58% vs. 28%)		Heart: $D_{mean}\downarrow$ : 17.7Gy, $V_{5, 10, 20, 30}\downarrow$ : 12.7%, 12.7%, 46%, 43.3%.		
Sumiya et al. <sup>27</sup>	54 vs. 15	PBT vs. 3D-CRT	-	WTB: $*V_{5, 10, 20, 30, 40, 50}$ : 10.1%, 8.6%, 16.5%, 26.6%, 19%, 5.3%,	-	
2021		PTV: 56-70Gy/28-35F		V <sub>60</sub> ↓: 0.4%.		
		Site: M+L (80% vs. 67%)				
Lin et al. <sup>28</sup>	46 vs. 61	PBT (80% PSPT) vs. IMRT	Lung: D <sub>mean</sub> <20Gy, V <sub>5</sub> <60%, V <sub>10</sub> <40%,	<sup>#</sup> Lung: *D <sub>mean</sub> ↓: 3.6Gy, *V <sub>5,20</sub> ↓: 21.7%, 5.2%.	PTV cov	/erage
2020		PTV: 50.4Gy/28F	$V_{20}\!<\!35\%;$	<sup>#</sup> Heart: *D <sub>mean</sub> ↓: 8.5Gy.	$\mathbf{SS}\uparrow$	

		Site: L (83% vs. 84%)	Heart: D <sub>mean</sub> <26Gy, V <sub>30</sub> <45%.		$^{\#}SC: D_{max}\downarrow: 0.1Gy.$	
Wang et al. <sup>29</sup>	159 vs. 320	PBT (91% PSPT) vs. IMRT	-		Heart: *D <sub>mean</sub> ↓: 9.1Gy, *V <sub>5, 30</sub> ↓: 45.4%, 8.1%.	-
2020		PTV: 50.4Gy/28F (med)				
		Site: L (138 vs. 288)				
Bhangoo et al. <sup>31</sup>	32 vs. 32	PBT (IMPT) vs. IMRT (4DCT)	Lung: D <sub>mean</sub> <15Gy, V <sub>20</sub> <20%;		$^{\text{#Lung: *D}_{mean}\downarrow: 5.3Gy, V_{20}\downarrow: 2\%.$	-
2020		PTV: 50Gy/25F (med)	Heart: Dmean<26Gy, V40<30%		<sup>#</sup> Heart: *D <sub>mean</sub> ↓: 11.2Gy, *V <sub>30</sub> ↓: 7%.	
		Site: L (78% vs. 94%)				
Macomber et al. <sup>34</sup>	16 vs. 39	PBT vs. IMRT/3D-CRT (21/18)	-		(vs. IMRT) Heart: $D_{mean}\downarrow$ : 16.1Gy, $V_{5, 40}\downarrow$ : 66%, 6%, $V_{50}\downarrow$ : 1%.	-
2018		PTV: 50.4Gy/28F			(vs. 3D-CRT) Heart: *D <sub>mean</sub> ↓: 25.1Gy, *V <sub>5,40,50</sub> ↓: 64%, 27%, 6%.	
		Site: L (82%)				
Xi et al. <sup>35</sup>	132 vs. 211	PBT vs. IMRT	Lung: D <sub>mean</sub> <20Gy, V <sub>20</sub> <35%;		Lung: *D <sub>mean</sub> ↓: 3.5Gy, *V <sub>5, 10, 20</sub> ↓: 19.7%, 9.1%, 7.1%.	PTV coverage
2017		PTV: 50.4Gy/28F (med)	Heart: V <sub>40</sub> <40%.		Heart: $D_{mean} \downarrow$ : 8.3Gy, $V_{30} \downarrow$ : 5.5%, $V_{40} \downarrow$ : 0.3%.	SS ↑
		Site: L (71% vs. 73%)				
Lin et al.37	111 vs. 469	PBT vs. 3D-CRT/IMRT (214/ 255)	Lung: D <sub>mean</sub> <20Gy, V <sub>20</sub> <35%;		(vs. 3D-CRT) Lung: *D <sub>mean</sub> ↓: 4.4Gy;	-
2017		PTV: 50.4Gy/28F	Heart: V <sub>40</sub> <40%.		Heart: *D <sub>mean</sub> ↓: 15.2Gy.	
		*Site: L (98% vs. 88%/95%)			(vs. IMRT) Lung: *D <sub>mean</sub> ↓: 3.4Gy;	
					Heart: *D <sub>mean</sub> ↓: 9.2Gy.	
Makishima et al. <sup>38</sup>	44	PBT (IMPT) vs. 3D-CRT	-		<sup>#</sup> (25 vs. 25) Lung: *D <sub>mean</sub> ↓: 3.6Gy, *V <sub>5, 10, 20</sub> ↓: 14.7%, 10%, 7.0%.	-
2015	(25 vs. 19)	PTV: 60Gy/30F (med)			Heart: *V <sub>30, 40, 50</sub> ↓: 41.8%, 36.5%, 23.5%.	
		Site: M (88%)			<sup>#</sup> (19 vs. 19) Lung: *D <sub>mean</sub> ↓: 8.0Gy *V <sub>5, 10, 20</sub> ↓: 26.7%, 17.9%, 13.4%.	
					Heart: *V <sub>30, 40, 50</sub> ↓: 46.2%, 46.1%, 13.5%.	
Zhu et al. <sup>46</sup>	246 vs. 500	PBT vs. PRT	-		(vs. photon) Lung: $D_{mean}\downarrow$ : 4.1Gy, $V_{5-40}\downarrow$ : 21.9%, 10.1%, 7.7%,	-
2021		PTV: 50.4Gy			$7.6\%$ , $2.8\%$ , $1.43\%$ , $0.72\%$ . $V_{45,50}$ : $0.2\%$ , $0\%$ .	
		Site: L (88% vs. 86%)			Heart: $D_{mean}\downarrow$ : 10.4Gy, $V_{5-45}\downarrow$ : 48.9%, 42.5%, 32%, 23.4%, 16.2%,	
					$10.6\%, 6.3\%, 3.4\%, 1.5\%; V_{50} \downarrow: 0.6\%.$	
Oonsiri et al.47	25	PBT (IMPT) vs. IMRT	-		Lung: *Dmean↓: 6.8Gy, *V5, 10, 15, 20, 30↓: 30%, 27.4%, 18.6%, 11.3%,	No SS change
2022		PTV: 60-66Gy/ F			$3.8\%$ , $V_{40}\downarrow$ : 0.5%;	
		Site: U+M (76%)			Heart: *Dmean↓: 6.5Gy. *V <sub>10, 20, 30, 40, 50</sub> ↓: 43.6%, 40.4%, 28.4%,	
					15.8%, 7.3%.	
Choi et al.49	15 vs. 16	PBT vs. PRT	-		Lung: *Dmean↓: 3.9Gy, *V <sub>10, 20</sub> ↓: 9.4%, 4.2%;	-
2022		PTV: 41.4Gy/28F			Heart: *Dmean↓: 13.6Gy. *V10, 30, 40↓: 25.4%, 33.5%, 22.9%.	
		Site: M+L (73% vs. 69%)				
Kato et al. <sup>50</sup>	10	PBT (IMPT) vs. VMAT	Lung: V <sub>20</sub> <30%, V <sub>30</sub> <20%;		Lung: *Dmean $\downarrow$ : 3.0Gy, *V <sub>5, 10, 20<math>\downarrow</math></sub> : 12.8%, 11.0%, 5.3%, V <sub>30, 40<math>\downarrow</math></sub> :	no SS CI, SS HI
2022		PTV: 60Gy/30F			1.5%, 0.4%.	$\downarrow$
		Site: U				
Zhang et al. <sup>51</sup>	11	PBT (IMPT) vs. IMRT	Lung: D <sub>mean</sub> ≤15Gy,	V₂0≤30%,	Lung: Dmean $\downarrow$ : 8.4Gy, V <sub>5, 10, 15, 20<math>\downarrow</math>: 40.8%, 26.6%, 19.9%, 15.4%.</sub>	-
2022		PTV: 50.4Gy/28F	V <sub>30</sub> ≤30%;		Heart: Dmean↓: 11.6Gy. *V <sub>10, 20</sub> ↓: 30.9%, 32.9%.	
		-	Heart: D <sub>mean</sub> $\leq$ 30Gy,	V₃₀≤40%,	(No statistical tests).	
			$V_{40} \le 30\%$ .			
Cui et al. <sup>52</sup>	30	PBT (IMPT) vs. IMRT/VMAT	Lung: V5<65%, V20<25%;		(vs. IMRT) Lung: *Dmean $\downarrow$ : 8.4Gy, *V <sub>5, 10, 15, 20<math>\downarrow</math>: 40.8%, 26.6%,</sub>	(vs. IMRT) no
2022		PTV: 60Gy/30F	Heart: D <sub>mean</sub> <26Gy, V <sub>30</sub> <46%.		19.9%, 15.4%. Heart: *Dmean $\downarrow$ : 11.6Gy. *V <sub>10,20</sub> $\downarrow$ : 30.9%, 32.9%, V <sub>5</sub> ,	SS CI, HI
		-			30, 40↓: 29.5%, 20.9%, 9.9%. SC: Dmax↓: 4.7Gy.	(vs. VMAT) SS
					(vs. VMAT) Lung: *Dmean↓: 7.3Gy, *V <sub>5,10,15</sub> ↓: 43.8%, 24.0%, 14.4%,	CI, HI ↑
					$V_{20}{\downarrow}{:}~8.8\%.~Heart{:}~*Dmean{\downarrow}{:}~14.6Gy,~*V_{20,~30,~40}{\downarrow}{:}~34.1\%,~28.3\%,$	
					21.33%, V <sub>5, 10</sub> ↓: 27.2%, 27.9%. SC: *Dmax↓: 8.9Gy.	

Key: All represent as mean  $\pm$  SD (except special explain). #: represent as median; ^: represent obtained from picture; \*: represent statistically significant; SS: statistically significantly; OARs: organs at risk; PTV: planning target volume; F: fraction; U/M/L: upper/middle/ lower thoracic; D<sub>mean</sub>: mean dose; V<sub>x</sub>: volume receiving  $\geq$ x Gy; PBT: proton beam therapy; PRT: photon radiotherapy; SFUD: single-field uniform dose; IMPT: intensity modulated proton therapy ; PSPT: passive scattering proton therapy; IMRT: intensity modulated proton therapy; CTV: clinical target volume; SC: spinal cord; LA(RA): left (right) atrium; LV(RV): left (right) ventricle; LCA: Left coronary artery; LMC: left main coronary artery; LAD: left anterior descending artery; LCX: left circumflex; RCA: right coronary artery; PC: Pericardium; HI: homogeneity index; CI: conformity index; VB: Vertebral Body (outline of the vertebrae, C2-L1); TV: thoracic vertebrae body (T1-T12); WTB: including the vertebrae of C5 to T12, all ribs, and the whole sternum.

eTable 2.	Results of C	Quality Asses	sment Usir	ig the Newcas	stle-Ottawa S	cale for Non	-RCT Studies	(Dosimetric	Parameters)
Reference	Represe-	Selection of	Ascertain-	Demonstration	Comparability	Assessment	Was follow-up	Adequacy	Total

Reference	Represe-	Selection of	Ascertain-	Demonstration	Comparability	Assessment	Was follow-up	Adequacy	Total
	ntativeness	the non-	ment of	that outcome of	of Cohorts on	of outcome	long enough for	of follow	score
	of the	exposed	exposure	the interest was	the basis of the		outcome to occur	up of	
	expose	cohort		not present at	design or			cohorts	
	cohort			start of study	analysis				
Zhang et al. <sup>11</sup>	☆	☆	☆	☆	☆☆	☆	\$	\$	9
2021									
Anakotta et	\$	\$	*	\$	**	\$	\$	\$	9
al. <sup>12</sup> 2020									
Celik et al. <sup>13</sup>	*	\$	4	\$	**	*	*	\$	9
2020			~						
Liu et al. <sup>14</sup>	*	*	*	*	*	*	*	*	8
2019	~	~	~	~	~	~	~	~	Ū.
Møller et al <sup>15</sup>	*	*	*	*	** **	*	*	*	9
2019	~	~	~	~	~~	~	~	~	2
Hirano et al <sup>16</sup>	x	J.	L	J.	J.	J.	A	L	8
2018	A	A	A	A	A	A	A	A	0
Shiraishi et al <sup>17</sup>	J.	x	L	J.	J.	x	A	L	8
2017	A	A	А	A	A	A	A	A	0
Warren et al <sup>18</sup>	x	x	L	J.	J.	J.	A	L	8
2017	×	ж	ж	ж	X	и	ж	ж	0
Warren et al <sup>19</sup>	J.	x	L	J.	J. J.	L	A	L	9
2016	A	A	А	A	AA	A	A	A	,
Ling et al <sup>20</sup>	*	*	*	*	** **	*	*	*	9
2014	6	6	6	6		6	6	6	-
Welsh et al. <sup>21</sup>	¢	\$	\$	\$	\$	\$	\$	\$	8
2011									
Zhang et al. <sup>22</sup>	☆	☆	☆	☆	\$	☆	\$	☆	8
2008									
Mu et al. <sup>23</sup>	☆	☆	☆	☆	**	☆	\$	☆	9
2011									
Sumiya et al.27	☆	☆	\$	☆	-	☆	☆	\$	7
2021									
Lin et al. <sup>28</sup>	☆	☆	☆	☆	☆	☆	☆	☆	8
2020									
Wang et al. <sup>29</sup>	☆	☆	☆	☆	-	☆	☆	☆	7
2020									
Bhangoo et	☆	☆	☆	☆	\$	☆	☆	☆	8
al. <sup>31</sup> 2020									
Xi et al. <sup>35</sup>	☆	☆	\$	*	*	\$	\$	\$	8
2017									
Lin et al. <sup>37</sup>	☆	☆	☆	☆	*	☆	☆	☆	8
2017									
Kato et al. <sup>50</sup>	☆	\$	\$	☆	**	\$	\$	\$	9
2022									
Zhang et al.51	☆	☆	☆	☆	**	☆	☆	☆	9

2022								
Cui et al. <sup>52</sup>	*	☆	☆	\$ **	☆	*	*	9
2022								

Reference	Represe-	Selection of	Ascertain-	Demonstration	Comparabilit	Assessment	Was follow-	Adequacy of	Total
	ntativeness of	the non-	ment of	that outcome of	y of Cohorts	of outcome	up long	follow up of	score
	the expose	exposed	exposure	the interest was	on the basis		enough for	cohorts	
	cohort	cohort		not present at	of the design		outcome to		
				start of study	or analysis		occur		
Suh et al. <sup>25</sup>	☆	☆	\$	☆	☆	☆	☆	☆	8
2021									
Sumiya et al. <sup>27</sup>	☆	☆	\$	☆	-	\$	-	☆	6
2021									
DeCesaris et al. <sup>30</sup>	☆	☆	☆	☆	-	☆	-	☆	6
2020									
Bhangoo et al. <sup>31</sup>	☆	\$	\$	☆	☆	☆	-	☆	7
2020									
Routman et al. <sup>32</sup>	☆	\$	\$	☆	-	☆	☆	☆	7
2019									
Shiraishi et al. <sup>33</sup>	☆	\$	\$	☆	☆	\$	☆	☆	8
2018									
Macomber et al. <sup>34</sup>	☆	\$	*	\$	☆	☆	-	☆	7
2018									
Xi et al. <sup>35</sup>	☆	\$	\$	☆	☆	\$	☆	☆	8
2017									
Fang et al. <sup>36</sup>	☆	\$	\$	☆	☆	☆	☆	☆	8
2018									
Makishima et al. <sup>38</sup>	☆	\$	\$	☆	-	\$	☆	☆	7
2015									
Zhu et al. <sup>46</sup>	☆	\$	\$	\$	☆	\$	☆	☆	8
2021									
Choi et al.49	☆	\$	<b>Å</b>	☆	☆	☆	-	☆	7
2022									

# eTable 3. Results of Quality Assessment Using the Newcastle-Ottawa Scale for Non-RCT Studies (Efficacy and Safety of Proton vs Photon Therapy)

### eTable 4. Results of Quality Assessment Using the Cochrane Collaboration's Tool (RCT)

Reference	Random sequence	Allocation	Blinding	Incomplete	Selective reporting	Other bias
	generation	concealment		outcome data		
Lin et al. <sup>28</sup>	Low	Unclear	High	Low	Low	Unclear
2020						

	eTable 5. Results of Qualit	y Assessment Using	g the MINORS	(Single-Group Tes	ts)
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Reference	A clearly	Inclusion of	Prospective	Endpoints	Unbiased	Follow-up	Loss to	Prospective	Total
	stated aim	consecutive	collection of	appropriate to	assessment of	period	follow up less	calculation of	score
		patients	data	the aim of the	the study	appropriate to	than 5%	the study size	
				study	endpoint	the aim of the			
						study			
Echeverria et al.4	2	2	2	2	0	2	2	0	12
2013									
Hirano et al. <sup>16</sup>	2	2	2	2	0	1	2	0	11
2018									
Parzen et al. <sup>39</sup>	2	1	2	2	0	2	2	0	11
2021									
Ogawa et al.40	2	2	2	2	0	2	2	0	12
2021									
Sato et al.41	2	2	2	2	0	1	2	0	11
2020									
Prayongrat et al.42	2	2	2	2	0	1	2	0	11
2017									
Zeng et al.43	2	2	1	1	0	1	2	0	9
2016									
Ishikawa et al.44	2	2	2	2	0	2	2	0	12
2015									
Lin et al.45	2	2	2	2	0	1	2	0	11
2012									
Rutenburg et al.53	2	2	2	2	0	1	2	0	11
2023									

## eTable 6. Pooled Analysis of Dose-Volume Parameters for OARs with Proton vs Photon Therapy

e lable 0. Pooled Analy	vs. 3D-CRT	vs. IMRT	vs. VMAT	Overall (Proton vs. Photon)	Egger's test (P value)
Lung					
Dmean (Gy)	-3.46 (-5.03, -1.88)	-4.66 (-5.70, -3.61)	-4.41 (-7.14, -1.68)	-4.42 (-5.38, -3.47)	0.959
	$I^2 = 77\%$	$I^2 = 88\%$	$I^2 = 96\%$	$I^2 = 93\%$	
V5 (%)	-8.83 (-13.55, -4.11)	-26.89 (-32.19, -21.58)	-25.93 (-47.42, -4.45)	-24.81 (-31.40, -18.21)	0.199
	$I^{2} = 0\%$	$I^2 = 86\%$	$I^2 = 98\%$	$I^2 = 95\%$	
V <sub>10</sub> (%)	-5.35 (-9.38, -1.32)	-12.87 (-17.91, -7.83)	-17.51 (-26.57, -8.45)	-12.92 (-16.84, -9.00)	0.359
	$I^2 = 0\%$	$I^2 = 83\%$	$I^2 = 79\%$	$I^2 = 82\%$	
V <sub>20</sub> (%)	-5.48 (-8.18, -2.78)	-7.16 (-9.77, -4.55)	-5.55 (-7.71, -3.38)	-6.52 (-8.24, -4.79)	0.511
	$I^2 = 0\%$	$I^2 = 89\%$	$I^2 = 64\%$	$I^2 = 84\%$	
V <sub>30</sub> (%)	-	-3.56 (-9.24, 2.12)	-	-3.05 (-5.86, -0.25)	*
		$I^2 = 95\%$		$I^2 = 89\%$	
$V_{40}(\%)$	-	-	-	-0.26 (-0.87, 0.34)	*
				$I^2 = 0\%$	
Heart					
D <sub>mean</sub> (Gy)	-15.08 (-16.36, -13.80)	-8.74 (-10.53, -6.94)	-8.86 (-12.02, -5.69)	-9.52 (-11.11, -7.94)	0.588
	$I^{2} = 0\%$	$I^2 = 90\%$	$I^2 = 89\%$	$I^2 = 92\%$	
V5 (%)	/	-45.29 (-51.22, -39.37)	-42.51 (-70.90, -14.13)	-45.06 (-51.18, -38.94)	*
		$I^2 = 81\%$	$I^2 = 92\%$	$I^2 = 82\%$	
<b>V</b> <sub>10</sub> (%)	/	-42.36 (-49.92, -34.79)	-	-39.52 (-47.45, -31.60)	*
		$I^2 = 66\%$		$I^2 = 72\%$	
V <sub>20</sub> (%)	-	-25.36 (-30.17, -20.55)	-	-26.60 (-31.90, -22.12)	*
		$I^2 = 41\%$		$I^2 = 43\%$	
V <sub>30</sub> (%)	-22.75 (-44.70, -0.81)	-13.07 (-16.67, -9.48)	-10.51 (-22.16, 114)	-13.89 (-17.84, -9.95)	< 0.001
	$I^2 = 92\%$	$I^2 = 85\%$	$I^2 = 93\%$	$I^2 = 93\%$	
V40 (%)	-20.54 (-42.39, 1.31)	-5.17 (-7.92, -2.43)	-9.23 (-32.05, 13.59)	-7.44 (-10.66, -4.22)	< 0.001
	$I^2 = 93\%$	$I^2 = 82\%$	$I^2 = 95\%$	$I^2 = 89\%$	
V <sub>50</sub> (%)	-	-1.92 (-7.57, 3.74)	/	-5.28 (-12.27, 1.70)	*
		$I^2 = 82\%$		$I^2 = 89\%$	
LV-D <sub>mean</sub> (Gy)	-	-12.43 (-19.11, -5.75)	-	-10.20 (-14.32, -6.08)	*
		$I^2 = 84\%$		$I^2 = 95\%$	
LAD-D <sub>mean</sub> (Gy)	-	-13.88 (-19.84, -7.93)	-	-11.24 (-17.31, -5.61)	*
		$I^2 = 90\%$		$I^2 = 99\%$	
ВМ					
D <sub>mean</sub> (Gy)	/	-	-3.00 (-5.25, -0.75)	-2.89 (-4.46, -1.32)	*
			$I^2 = 28\%$	$I^2 = 0\%$	
V <sub>10</sub> (%)	-	-	-11.22 (-16.34, -6.10)	-10.21 (-13.99, -6.42)	*
			$I^2 = 0\%$	$I^{2} = 0\%$	
V <sub>20</sub> (%)	-	-	-9.68 (-19.28, -0.08)	-10.33 (-16.20, -4.47)	*
			$I^2 = 77\%$	$I^2 = 69\%$	

D <sub>max</sub> (Gy)	-13.52 (-23.56, -3.48)	-7.14 (-10.95, -3.34)	-3.86 (-9.39, 1.67)	-6.93 (-9.73, -4.13)	0.097
	$I^2 = 81\%$	$I^2 = 92\%$	$I^2 = 89\%$	$I^2 = 91\%$	

Key: All represent mean and 95%CI (confidence interval); /: represent no one study; -: represent only one study; \*: represent included studies less than ten (P <0.05, represent significant publication bias);  $D_{mean}$ : mean dose;  $V_x$ : percentage of volume receiving  $\geq x$  Gy; LV: left ventricle; LAD: left anterior descending artery; BM: bone marrow; SC: spinal cord; Heart- $V_{30}$ ,  $V_{40}$  observed to have publication bias by Egger's test (P <0.05), there were two (results dose not significantly changed) and zero potential studies added by the trim-and-fill method.

e table 7. 1 00leu Analysis of	Acute	Late	Unknown	Total
RE				
G2+	1.69 (0.76, 3.75)	/	-	1.11 (0.76, 1.63)
	$I^2 = 0\%$			$I^2 = 0\%$
G3+	1.15 (0.40, 3.29)	/	-	0.84 (0.48, 1.46)
	$I^2 = 0\%$			$I^2 = 0\%$
G4+	-	/	-	0.53(0.02, 13.1)
				$I^2 = Not applicable$
RP				
G2+		-		0.40 (0.17, 0.97)
				$I^2 = 0\%$
G3+	_		-	0.45(0.12, 1.67)
				$I^2 = 0\%$
G4+	-	-	-	0.80 (0.07, 8.88)
				$I^2 = Not applicable$
PE				
G2+	/	0.55 (0.10, 2.91)		0.73 (0.32, 1.65)
		$I^2 = 35\%$		$I^2 = 35\%$
G3+	-	-	-	0.28 (0.06, 1.32)
				$I^2 = 0\%$
G4+		-	-	Not estimable
PCE				
G2+	/	0.15 (0.01, 2.08)		0.20 (0.04, 0.96)
		$I^2 = 71\%$		$I^2 = 44\%$
G3+	-		-	0.34 (0.06, 2.06)
				$I^2 = 0\%$
G4+	-	-	-	Not estimable
lymphocytopenia				
G2+		/	/	
G3+	-	/	/	-
G4+	0.35 (0.28, 0.45)	/	/	0.35 (0.28, 0.45)
	$I^2 = 0\%$			$I^2 = 0\%$

Key: All presented as OR (odds ratio) and 95%CI (confidence interval); /: represent no one study; -: represent no sufficient data to analysis; G2+/3+/4+: toxicity grade  $\geq 2/3/4$ ; RE: radiation related esophagitis; RP: radiation pneumonitis; PE: Pleural effusion; PCE: pericardial effusion.

	Acute	Late	Unknown	Total
G2+				
RE	0.51 (95%CI: 0.35, 0.66)	/	0.46 (95%CI: 0.39, 0.53)	0.50 (95%CI: 0.40, 0.59)
	$I^2 = 68.7\%$		٨	$I^2 = 60.8\%$
RP	0.03 (95%CI: 0.00, 0.17)	0.00 (95%CI: 0.00, 0.01)	0.04 (95%CI: 0.02, 0.07)	0.02 (95%CI: 0.00, 0.06)
	$I^2 = 91.5\%$	$I^2 = 0\%$	٨	$I^2 = 83.4\%$
PE	/	0.03 (95%CI: 0.00, 0.08)	-	0.04 (95%CI: 0.02, 0.07)
		٨		$I^2 = 0\%$
PCE	0.00 (95%CI: 0.00, 0.04)	0.05 (95%CI: 0.01, 0.11)	-	0.03 (95%CI: 0.00, 0.07)
	۸	$I^2 = 57.8\%$		$I^2 = 62.7\%$
G3+				
RE	0.08 (95%CI: 0.04, 0.15)	-	0.11 (95%CI: 0.07, 0.16)	0.08 (95%CI: 0.05, 0.12)
	$I^2 = 63.6\%$		۸	$I^2 = 57.1\%$
G4+				
lymphocytopenia	0.17 (95%CI: 0.07, 0.30)	/	/	0.17 (95%CI: 0.07, 0.30)
	$I^2 = 93.8\%$			$I^2 = 93.8\%$

Key: CI: confidence interval; /: represent no one study; -: represent no sufficient data to analysis; ^: because included studies  $\leq 3$  (after double-arcsine transformations); G2/3/4+: toxicity grade  $\geq 2/3/4$ ; RE: radiation related esophagitis; RP: radiation pneumonitis; PE: Pleural effusion; PCE: pericardial effusion.