

## 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

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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]
- #2. ((((((((((((((Esophageal Neoplasm) OR (Neoplasm, Esophageal)) OR (Esophagus Neoplasm)) OR (Esophagus Neoplasms)) OR (Neoplasm, Esophagus)) OR (Neoplasms, Esophagus)) OR (Neoplasms, Esophageal)) OR (Cancer of Esophagus)) OR (Cancer of the Esophagus)) OR (Esophagus Cancer)) OR (Cancer, Esophagus)) OR (Cancers, Esophagus)) OR (Esophagus Cancers)) OR (Esophageal Cancer)) OR (Cancer, Esophageal)) OR (Cancers, Esophageal)) OR (Esophageal Cancers)
- #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 Radiation Therapy)
- #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

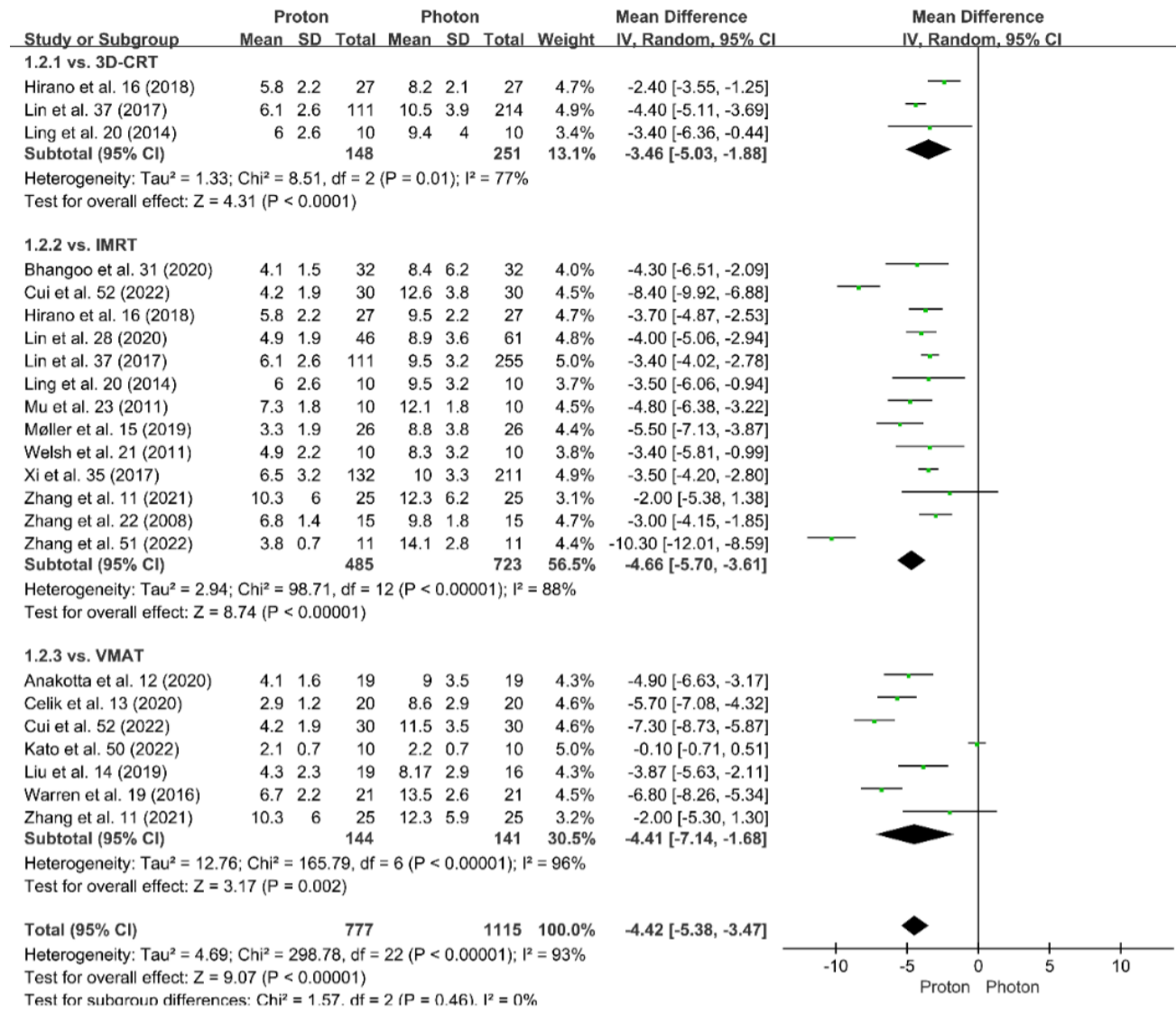
CNKI

(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')

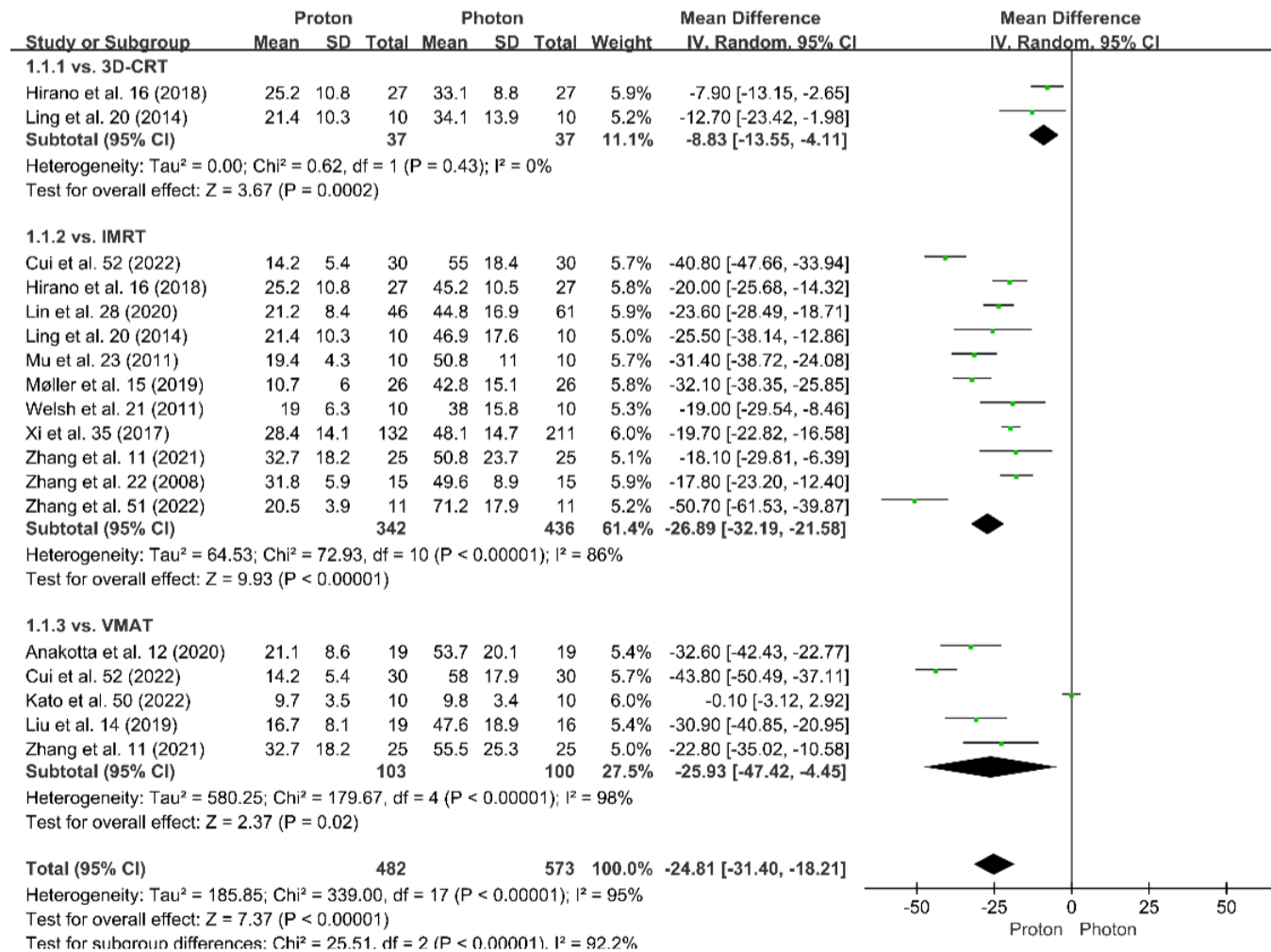
TKA: 篇文摘; %: 模糊检索

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

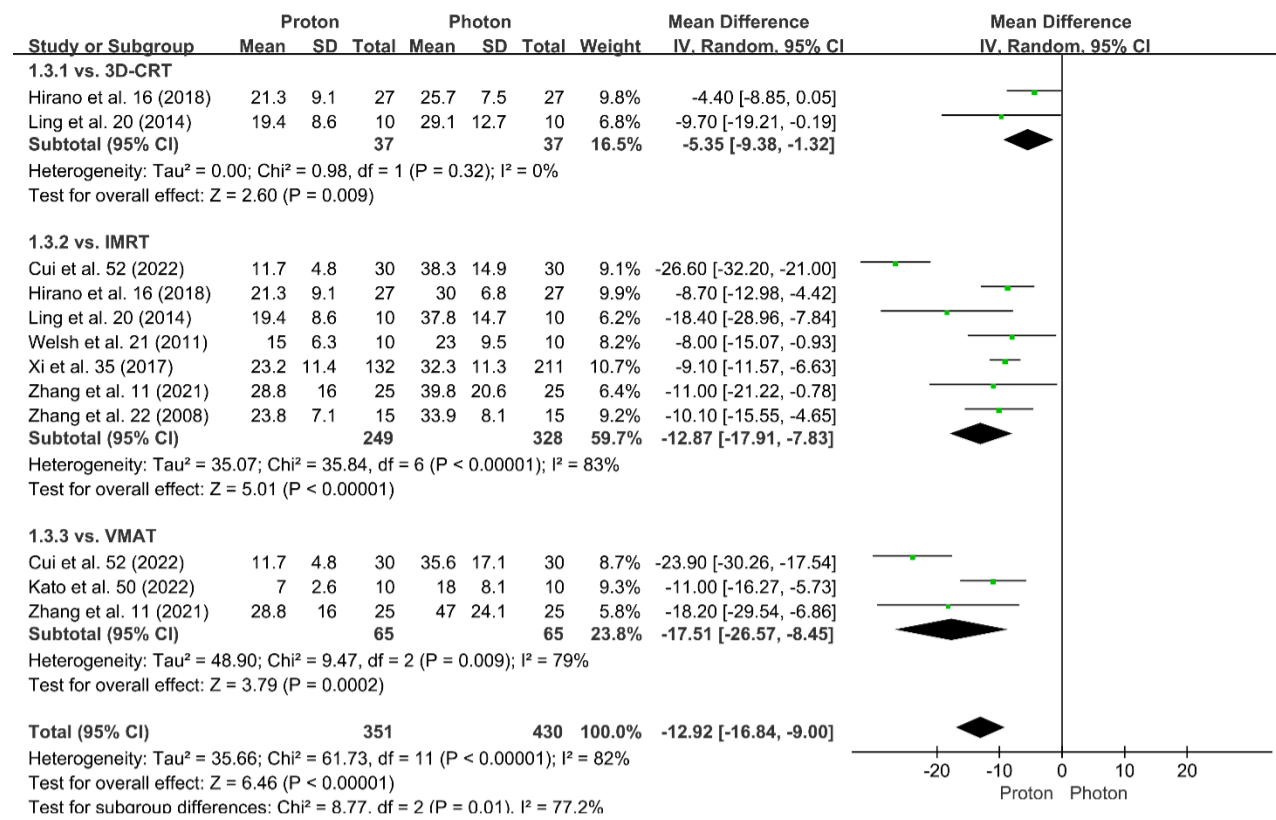
a) Lung- $D_{mean}$



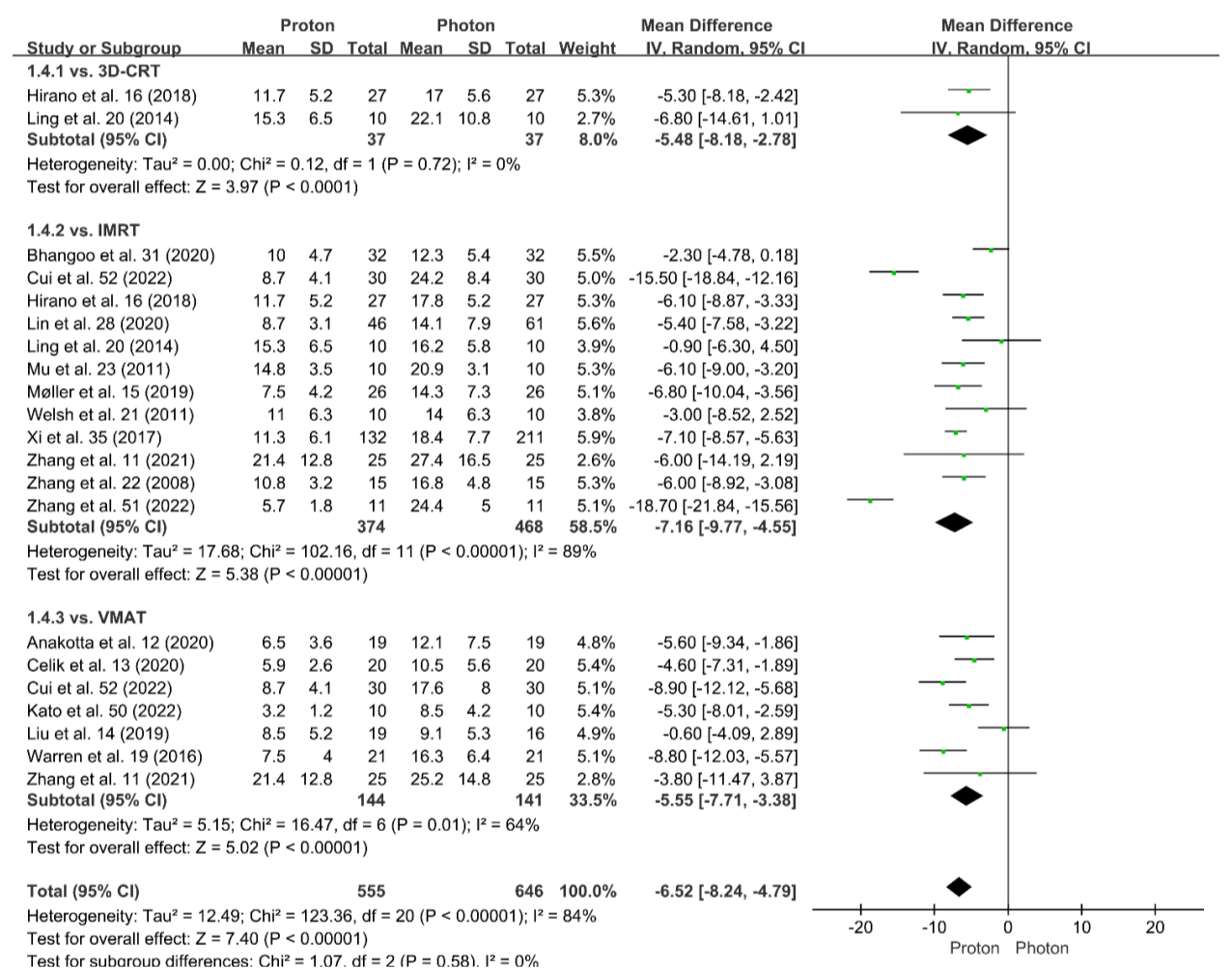
b) Lung- $V_5$



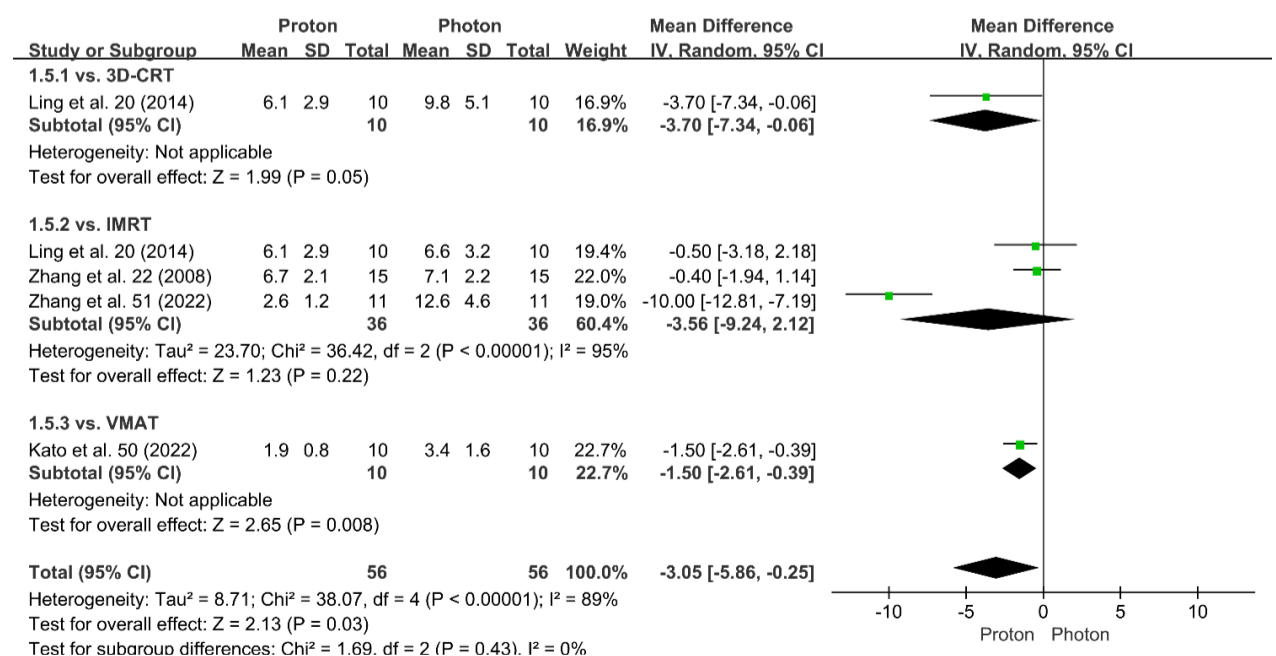
c) Lung-V<sub>10</sub>



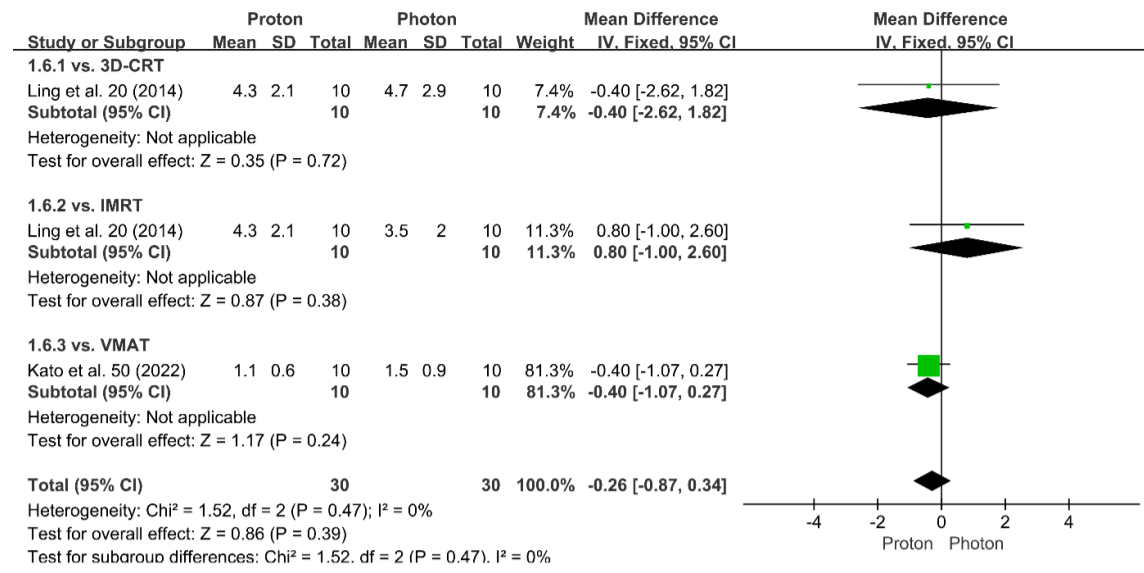
d) Lung-V<sub>20</sub>



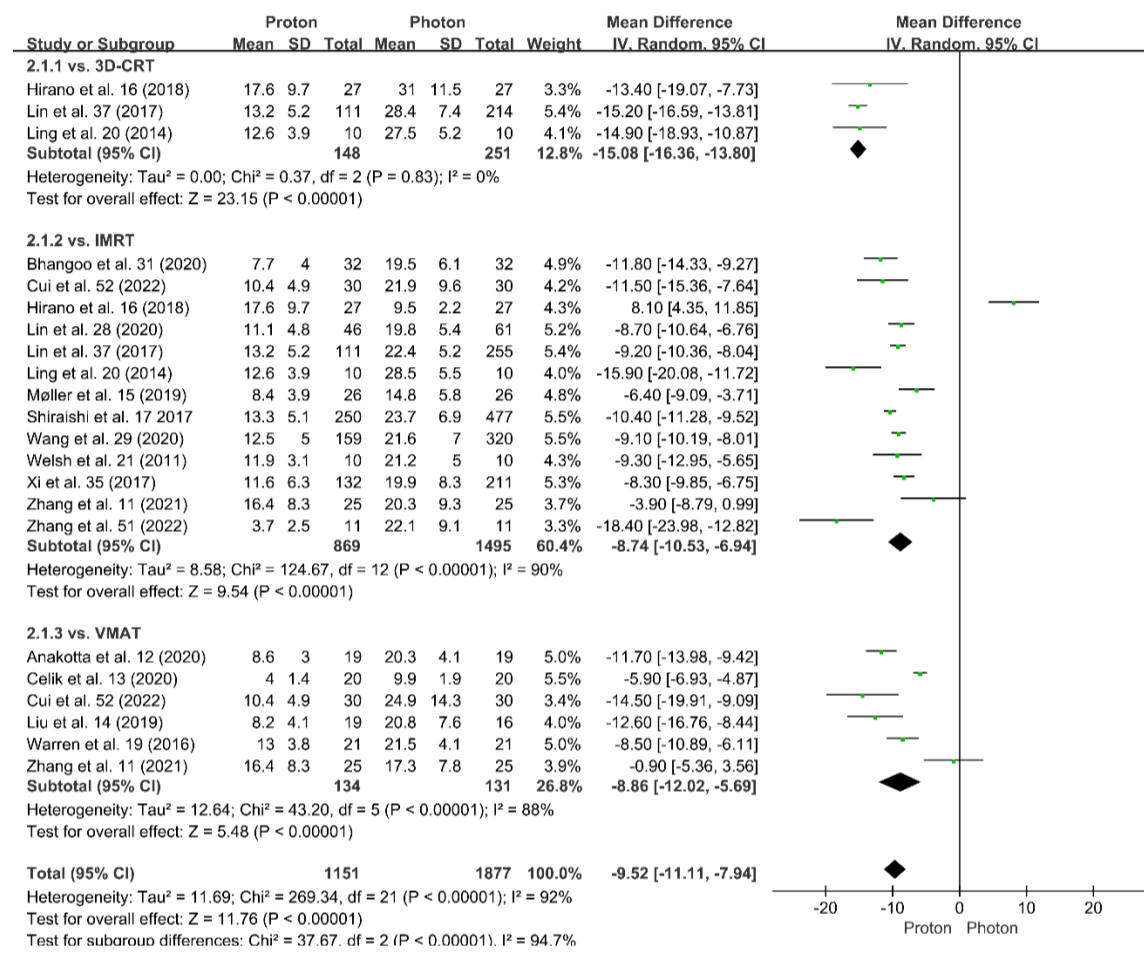
e) Lung-V<sub>30</sub>



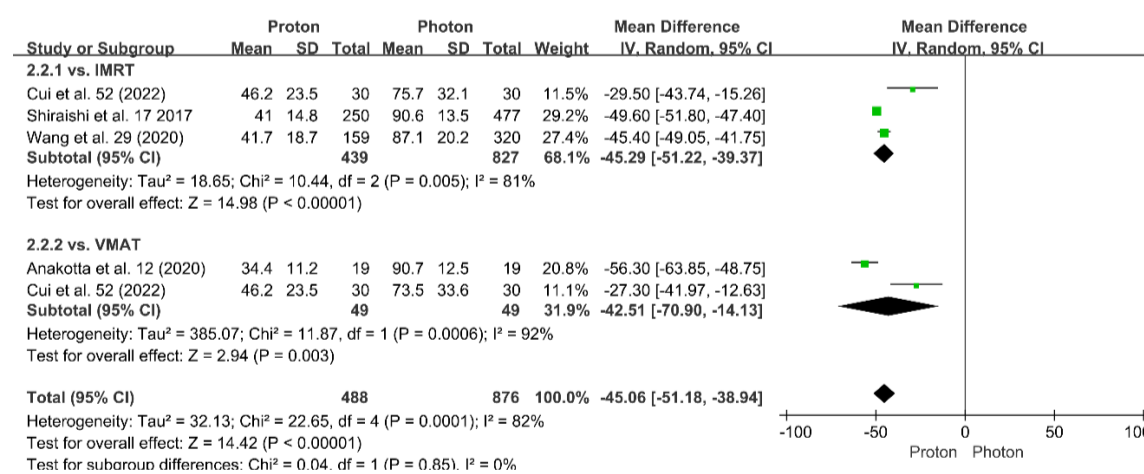
f) Lung-V<sub>40</sub>



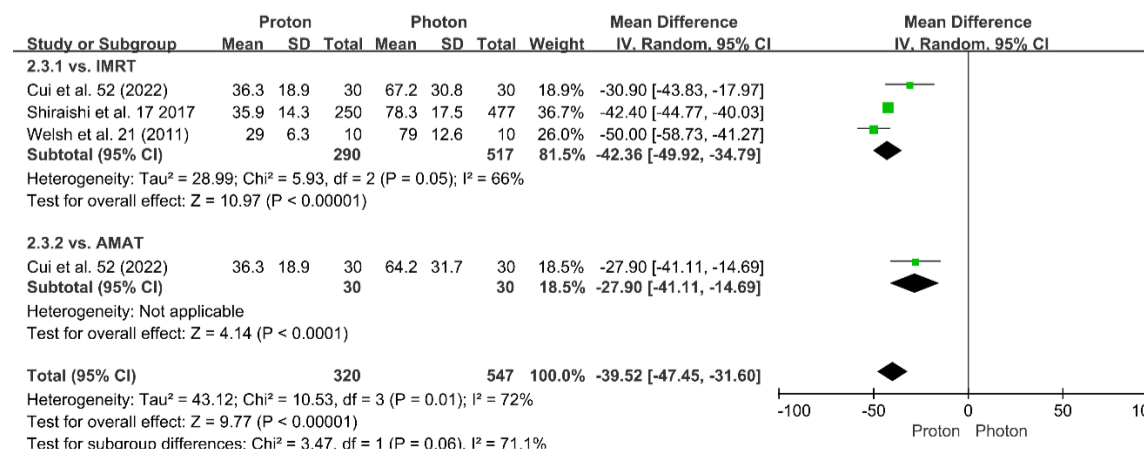
g) Heart-MLD



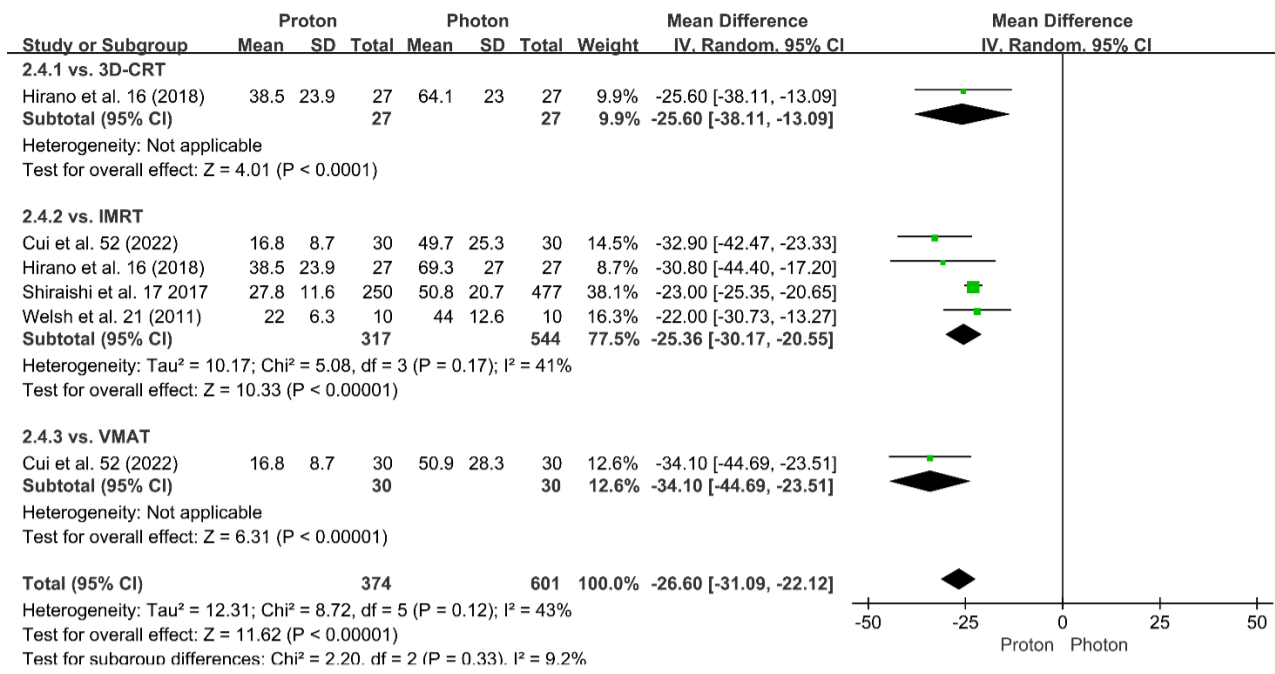
h) Heart-V<sub>5</sub>



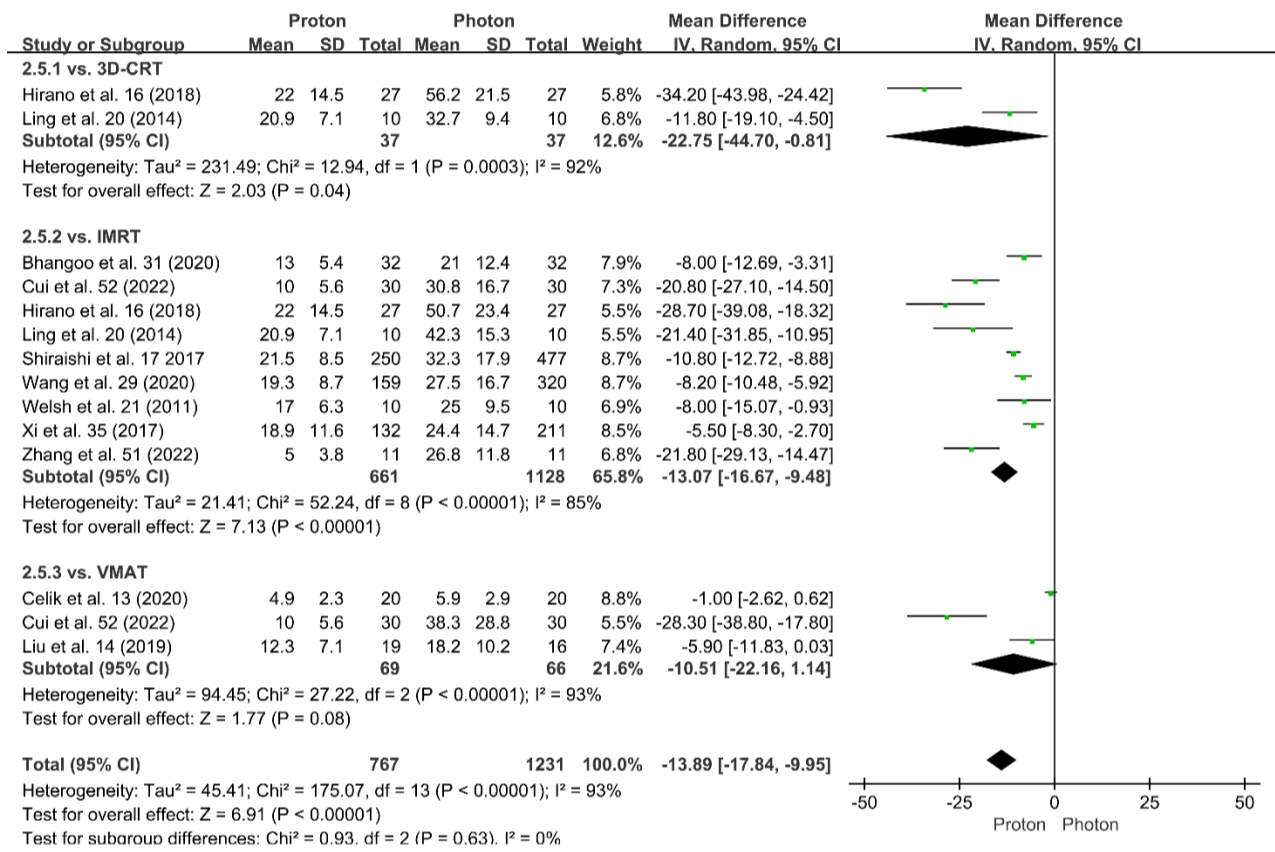
i) Heart-V<sub>10</sub>



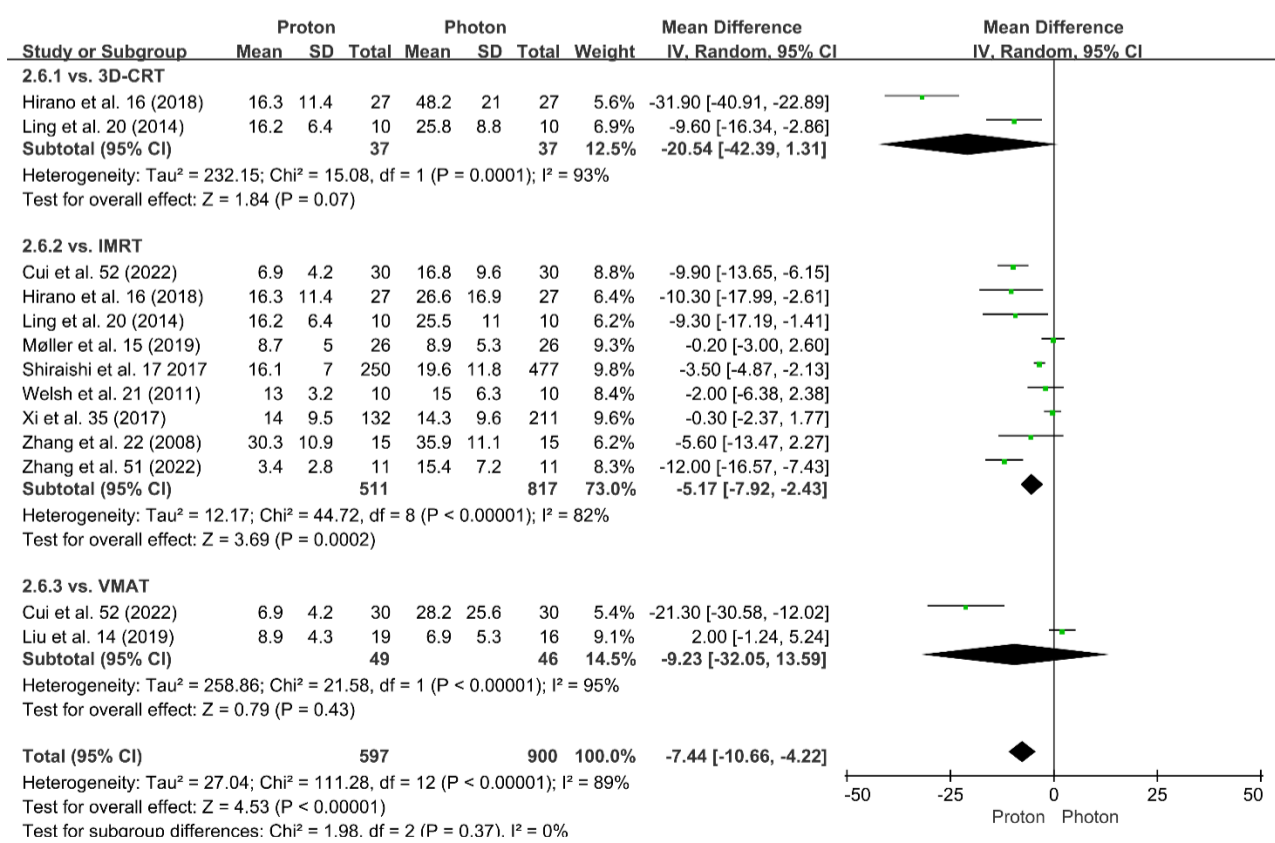
j) Heart-V<sub>20</sub>



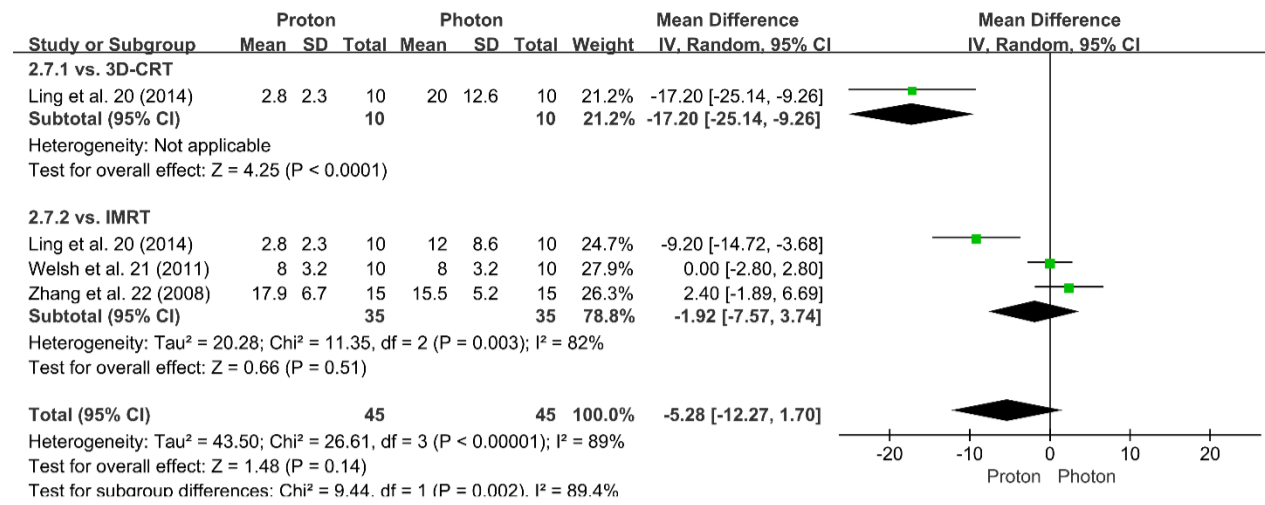
k) Heart-V<sub>30</sub>



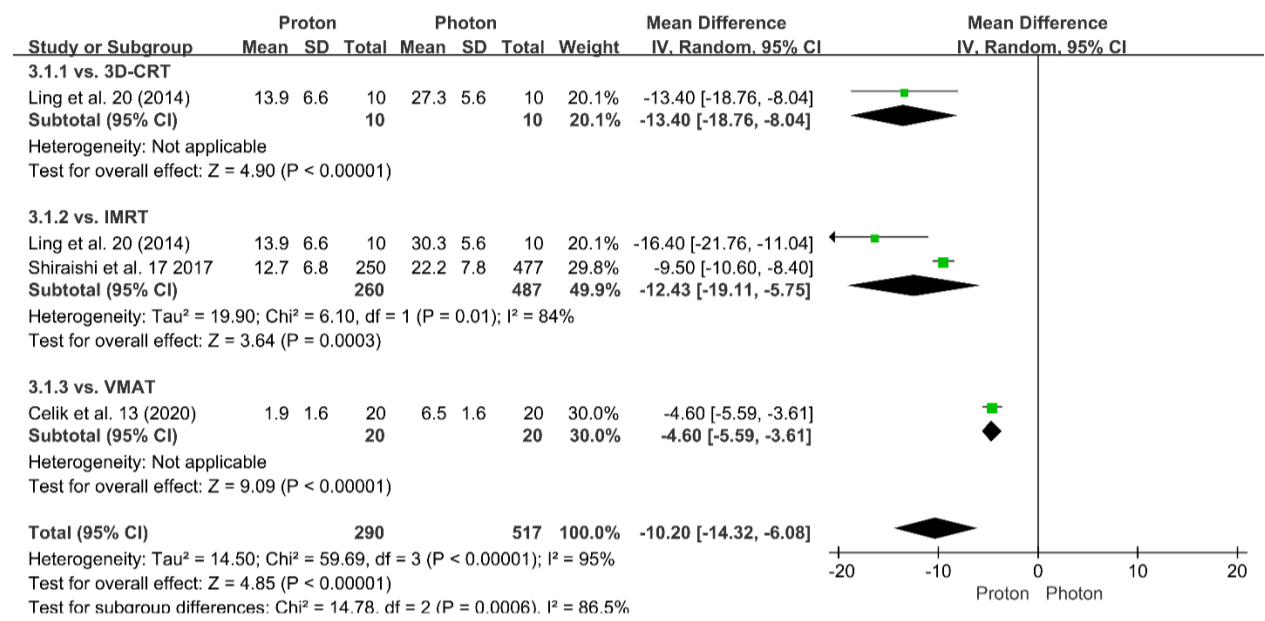
l) Heart-V<sub>40</sub>



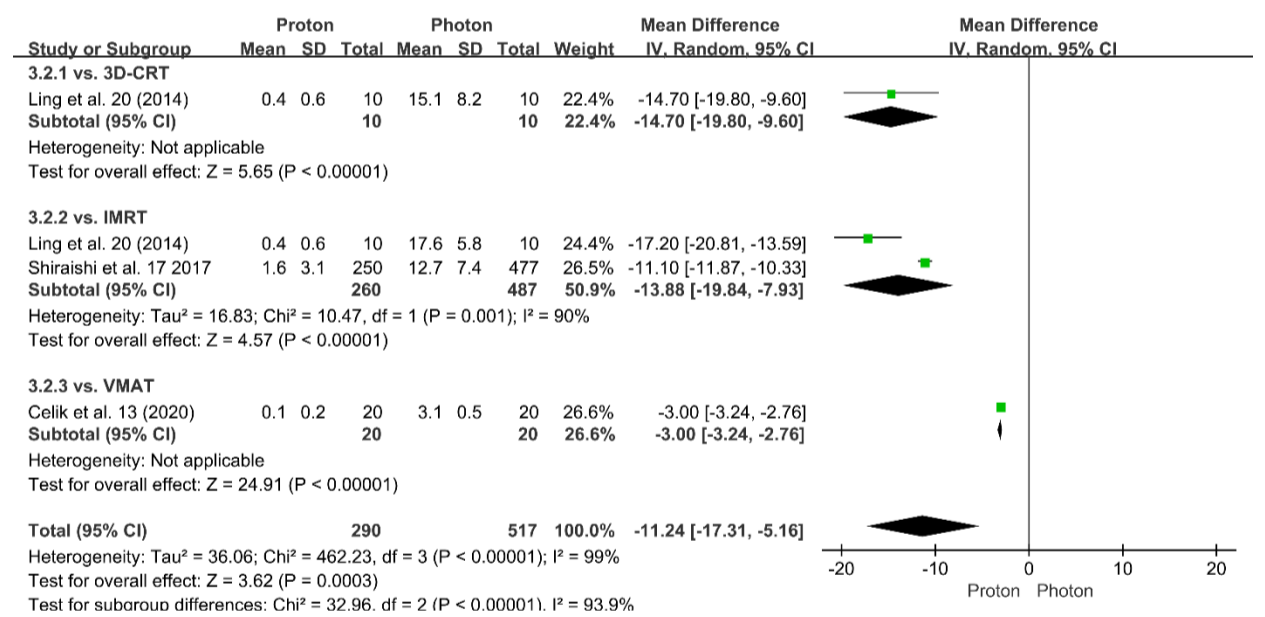
m) Heart-V<sub>50</sub>



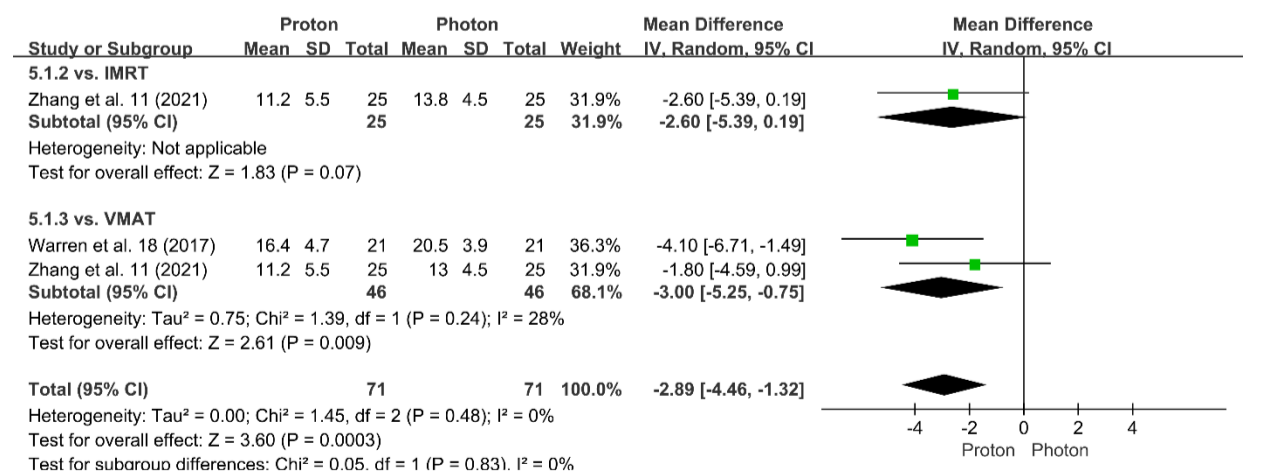
n) Left ventricle (LV)-D<sub>mean</sub>



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

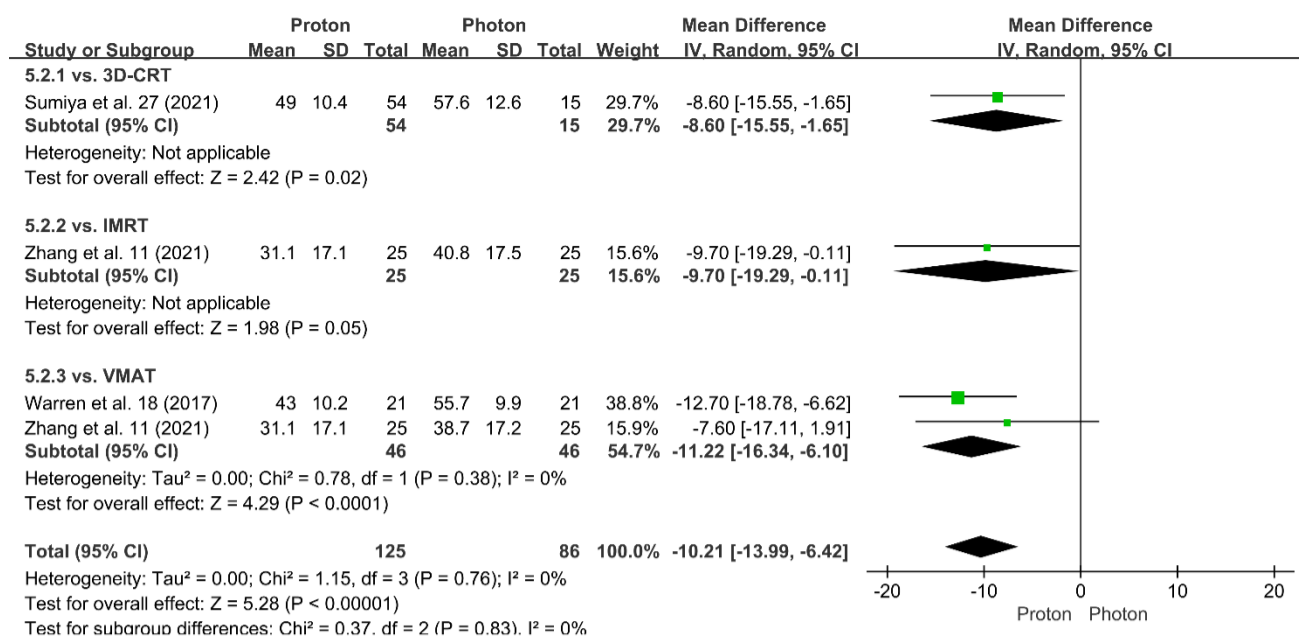


p) BM-D<sub>mean</sub>

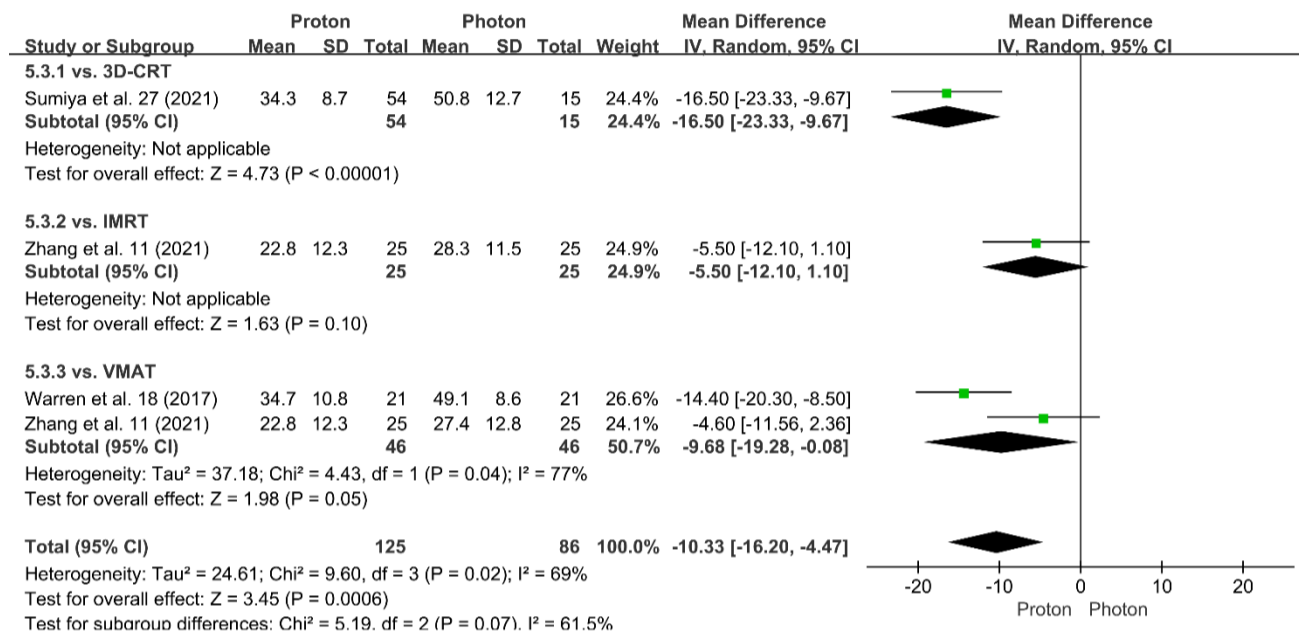


q) BM-V<sub>10</sub>

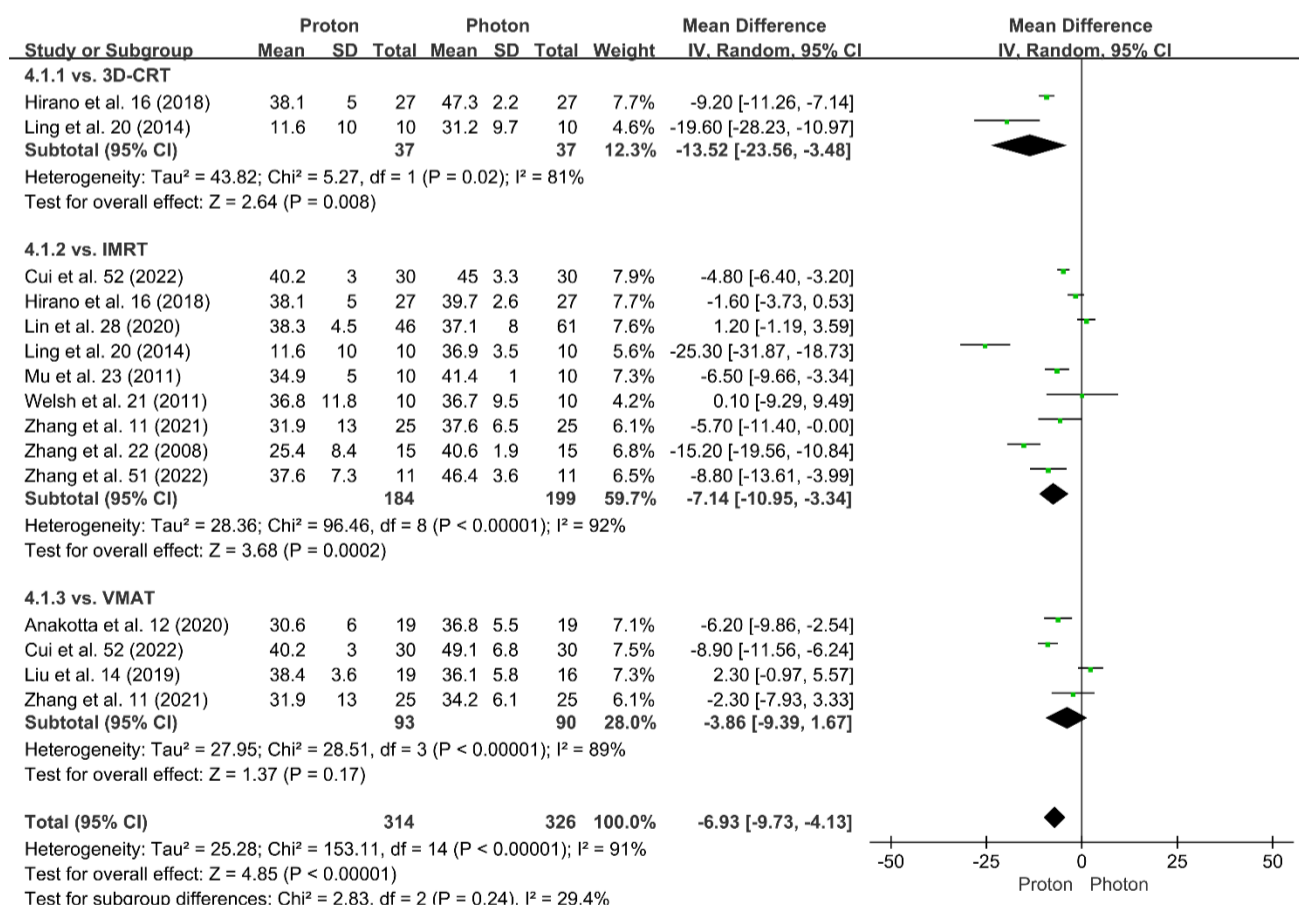




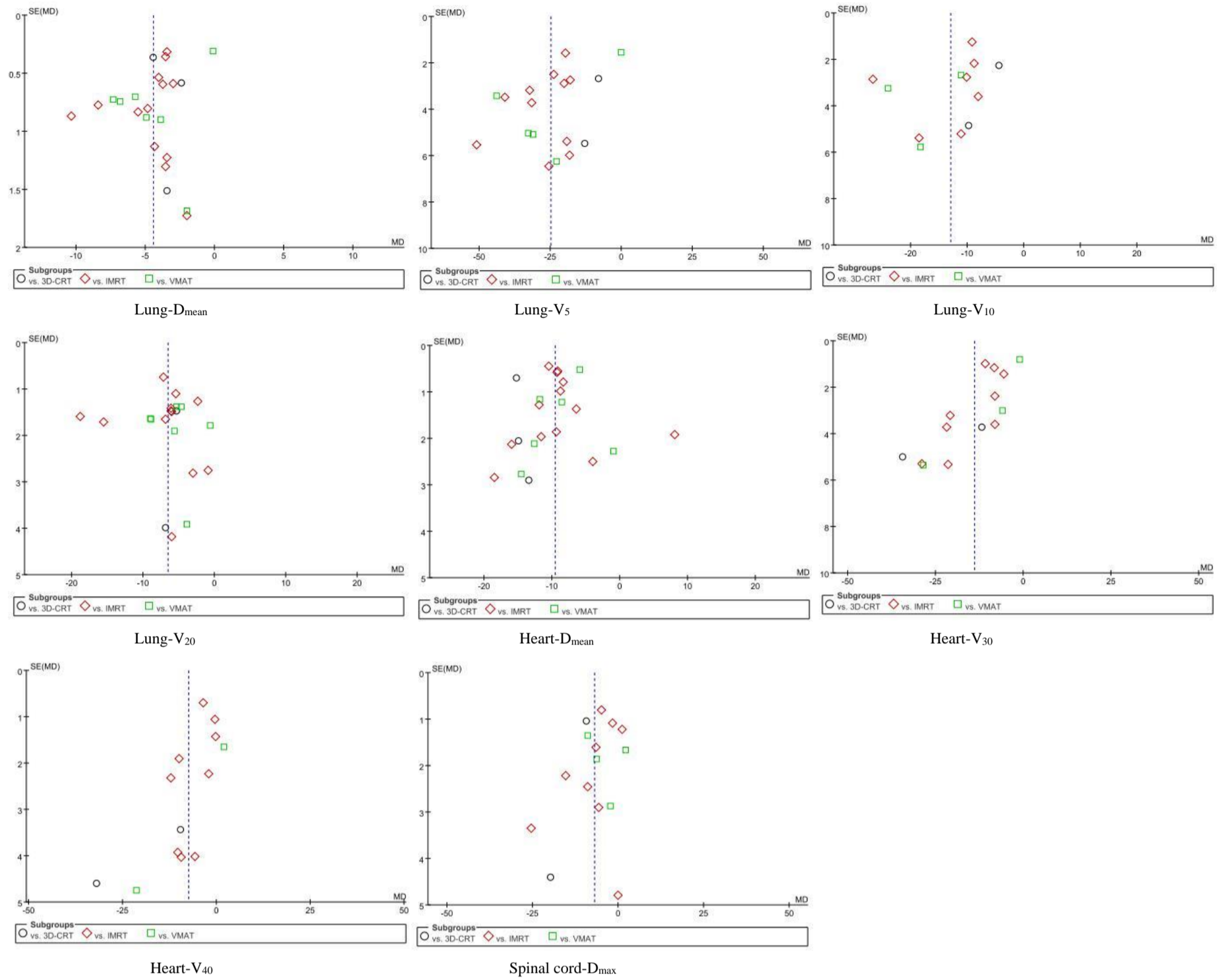
r) BM-V<sub>20</sub>



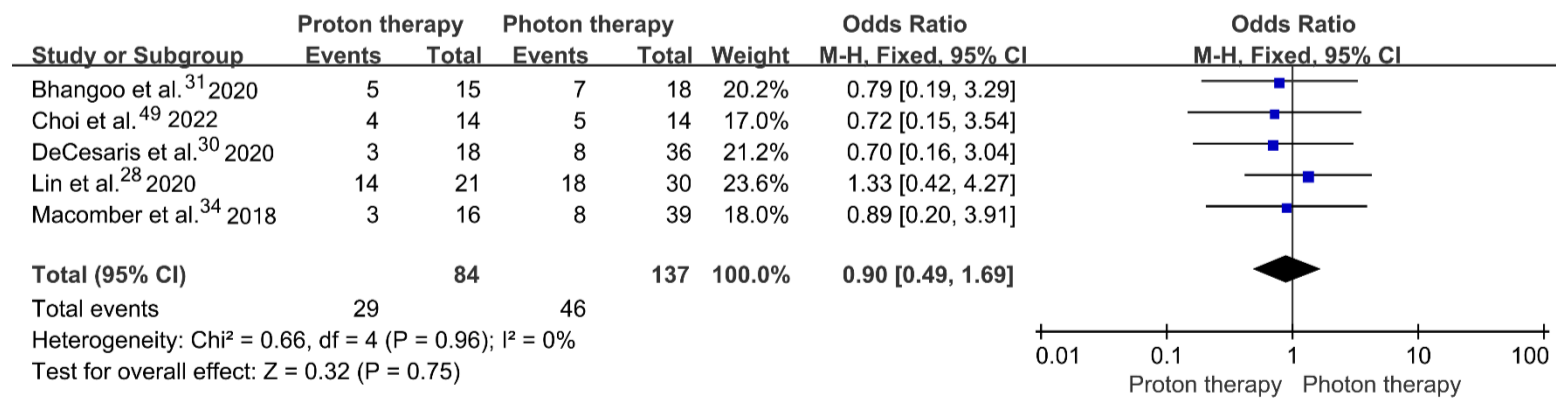
s) SC-D<sub>max</sub>



**eFigure 2.** Funnel Plot of Dose-Volume Parameters for OARs with Proton vs Photon Therapy (≥10 Articles)

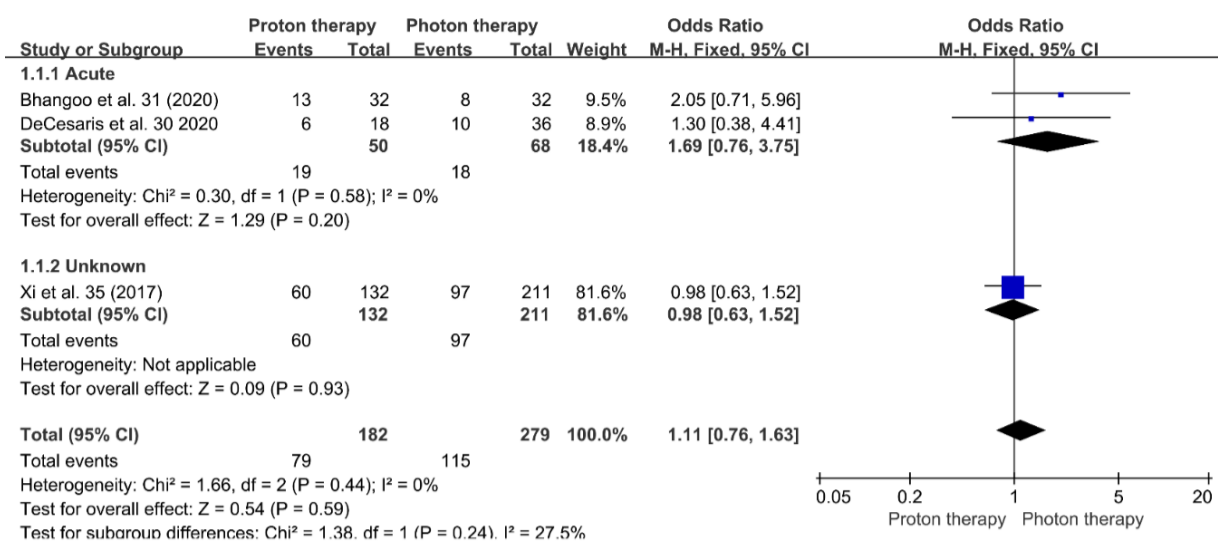


**eFigure 3.** Pooled Analysis of pCR (Proton vs Photon Therapy)

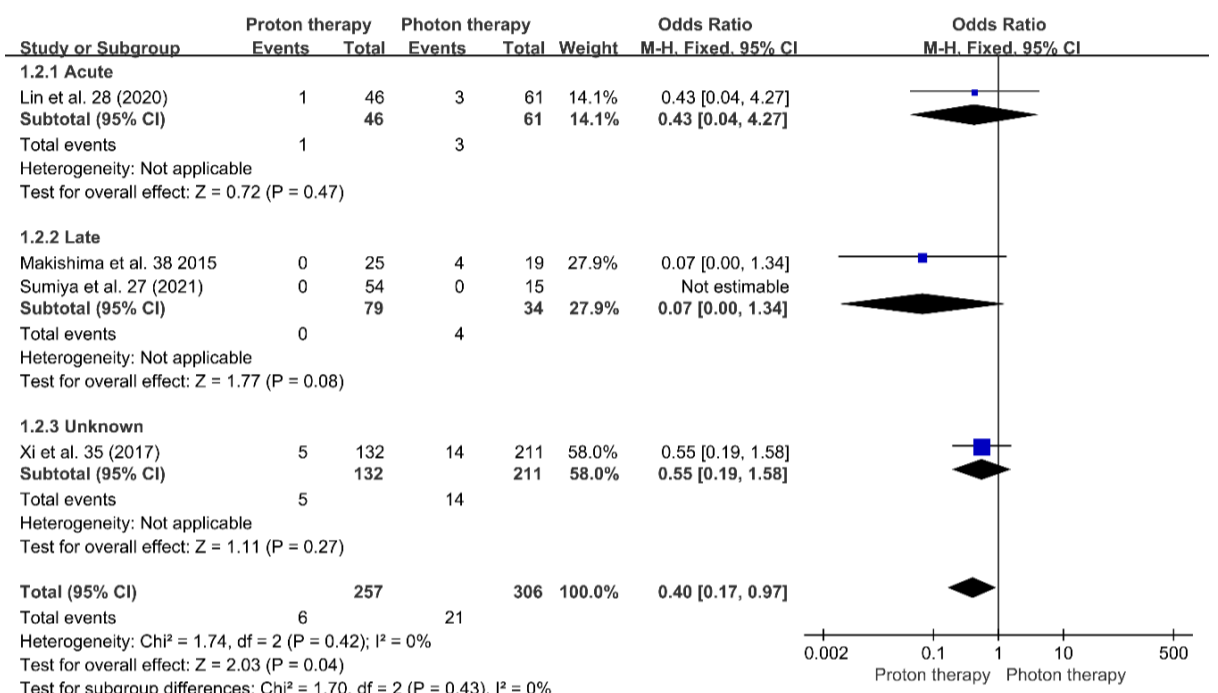


**eFigure 4.** Forest Plots of the Incidence of Toxic Effects in the Proton and Photon Therapy Groups (Described as

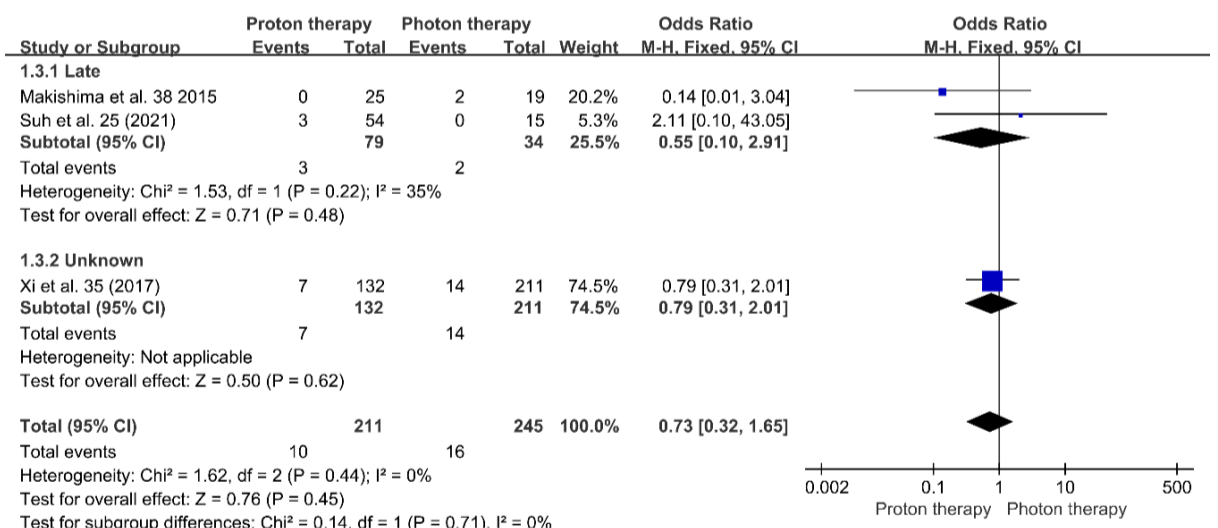
a) G2+ RE



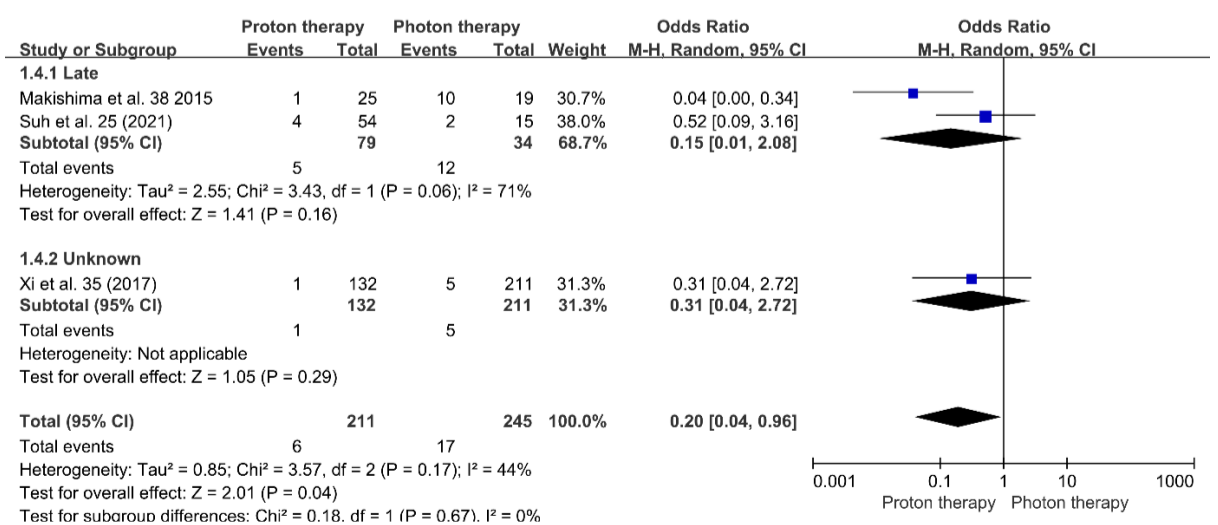
b) G2+ RP



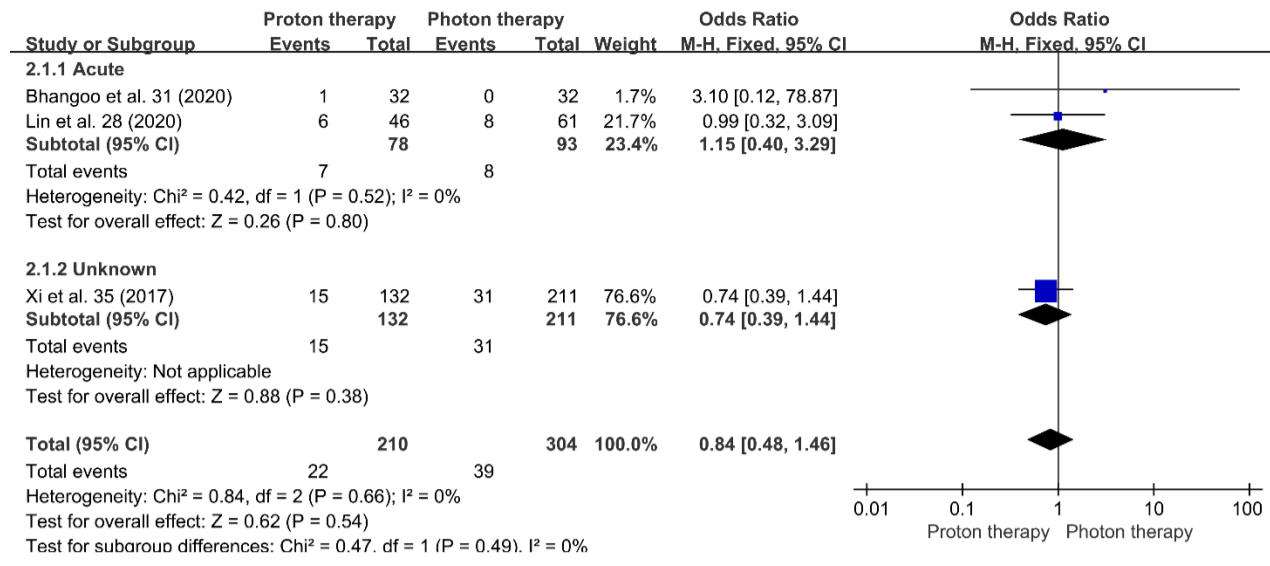
c) G2+ PE



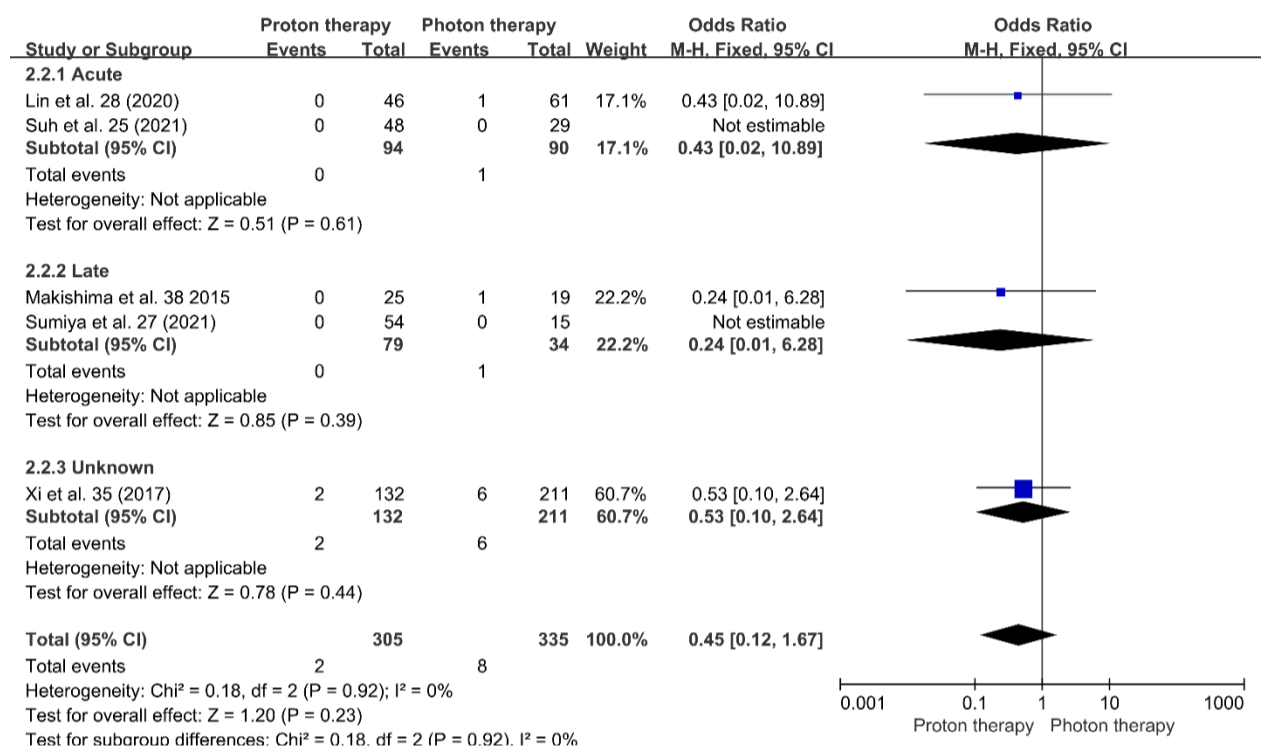
d) G2+ PCE



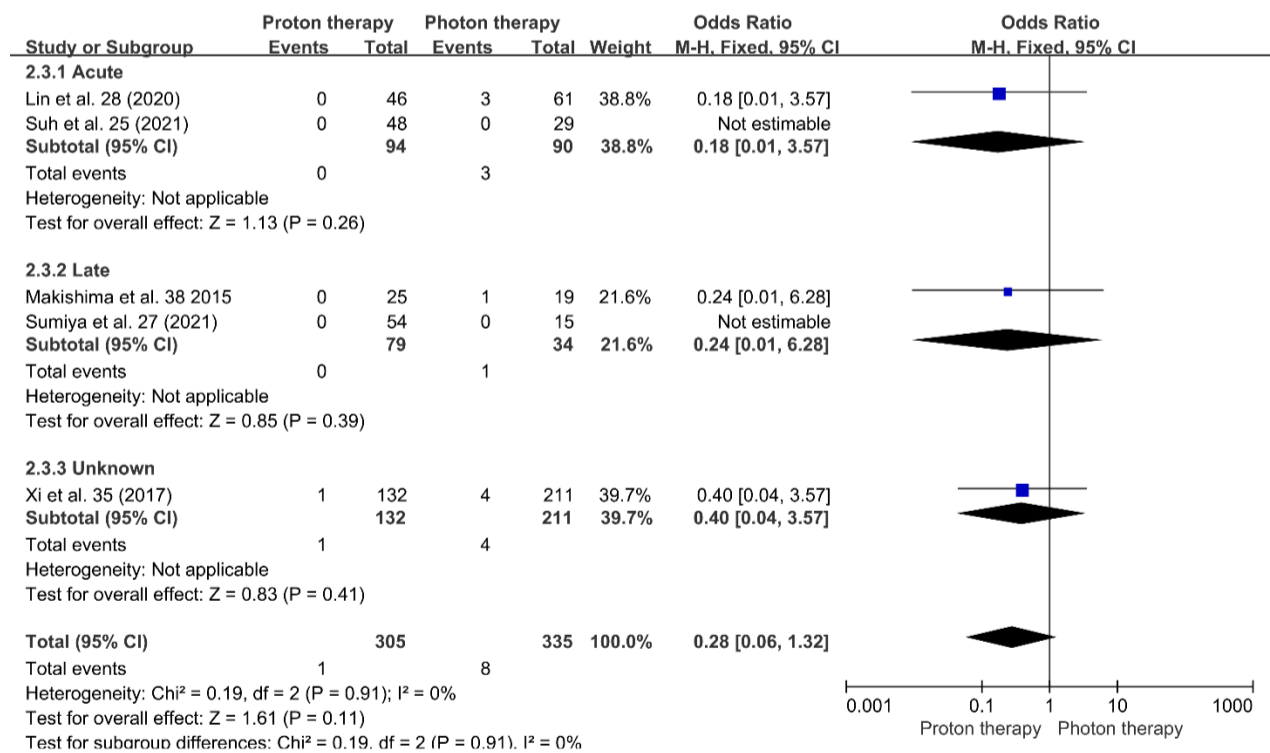
e) G3+ RE



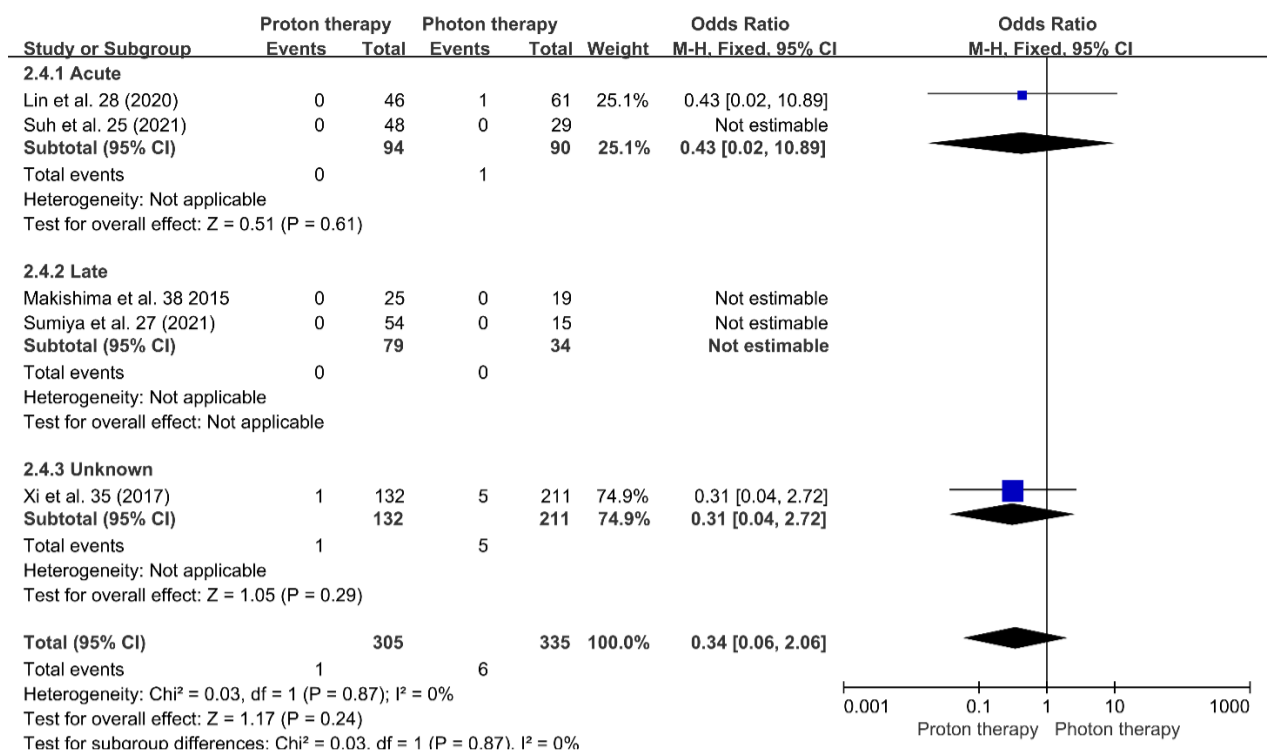
f) G3+ RP



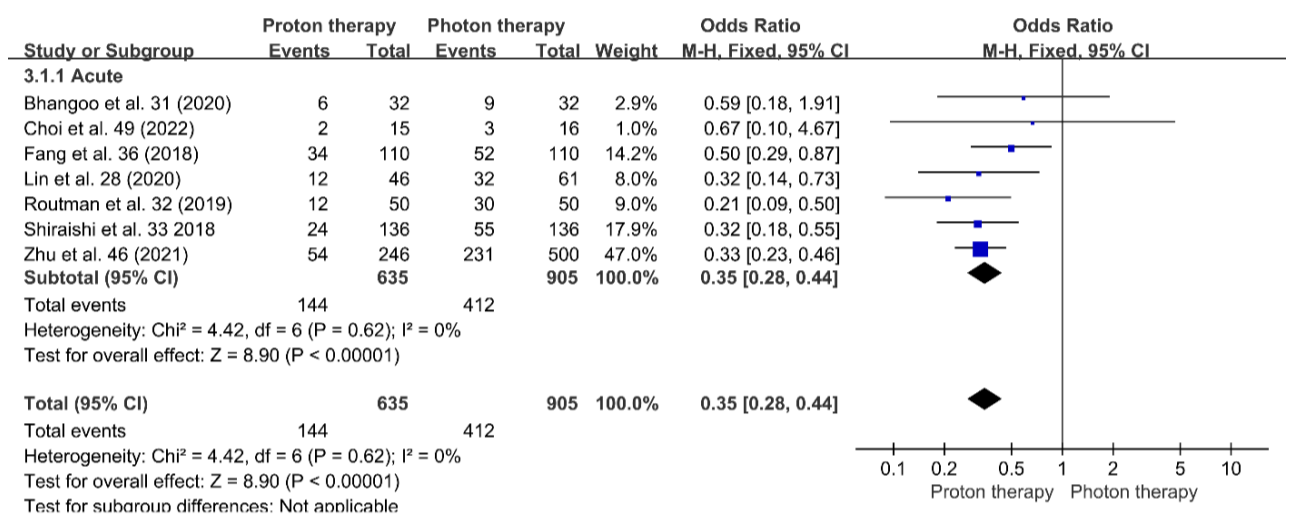
g) G3+ PE



h) G3+ PCE

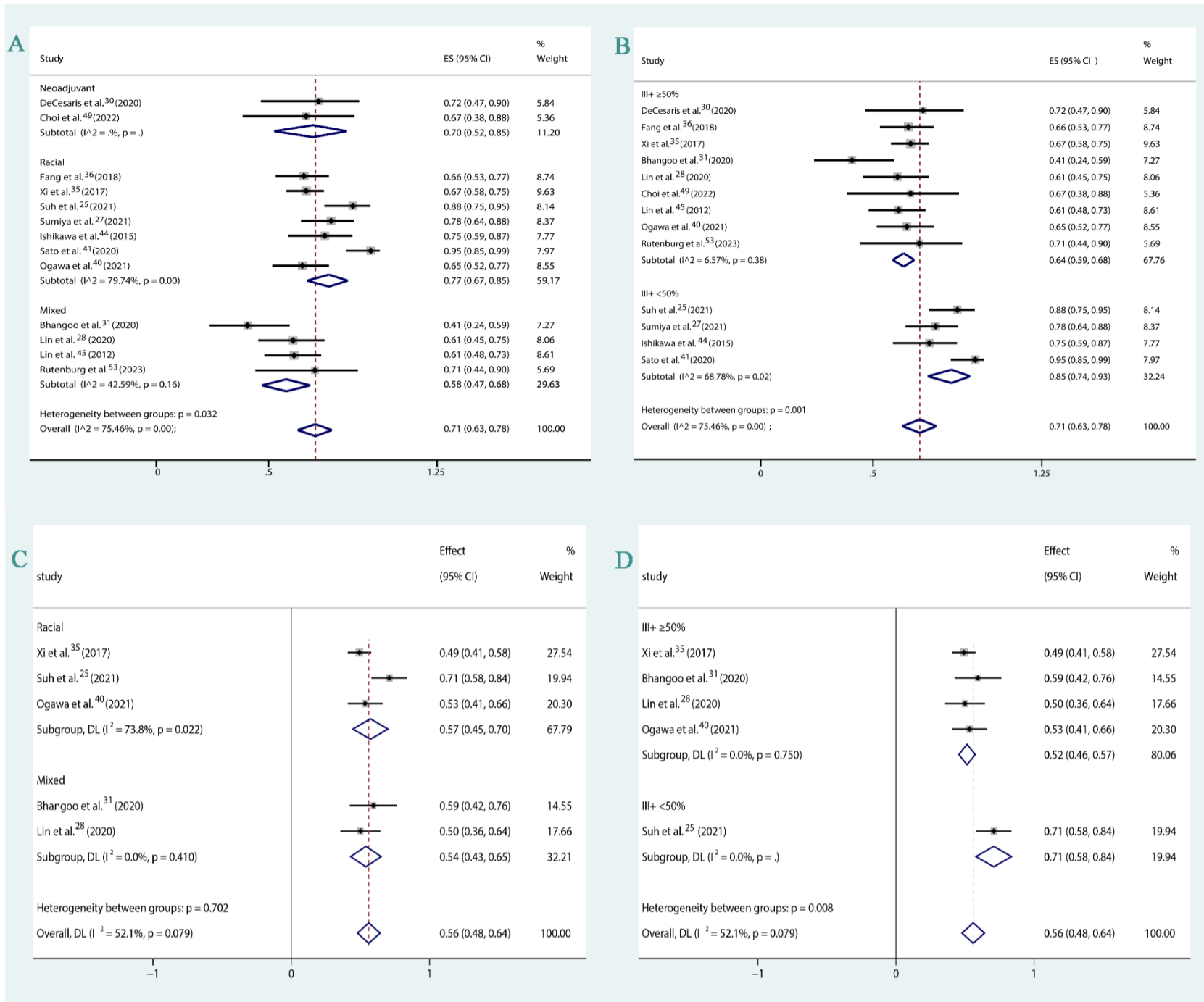


i) G4+ lymphocytopenia

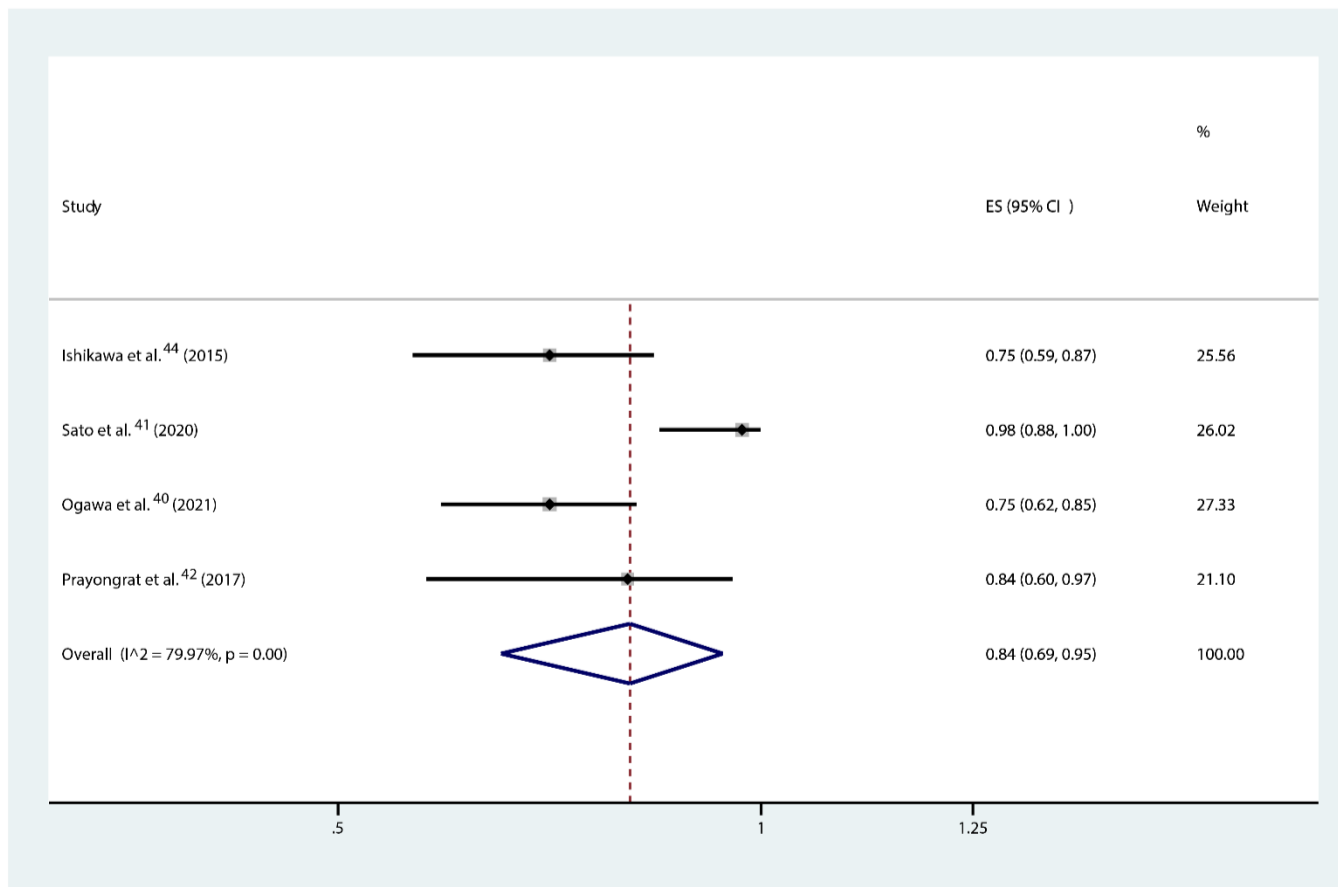


**eFigure 5.** Example of Single-Rate Pooled Analysis of OS and PFS for Proton Therapy

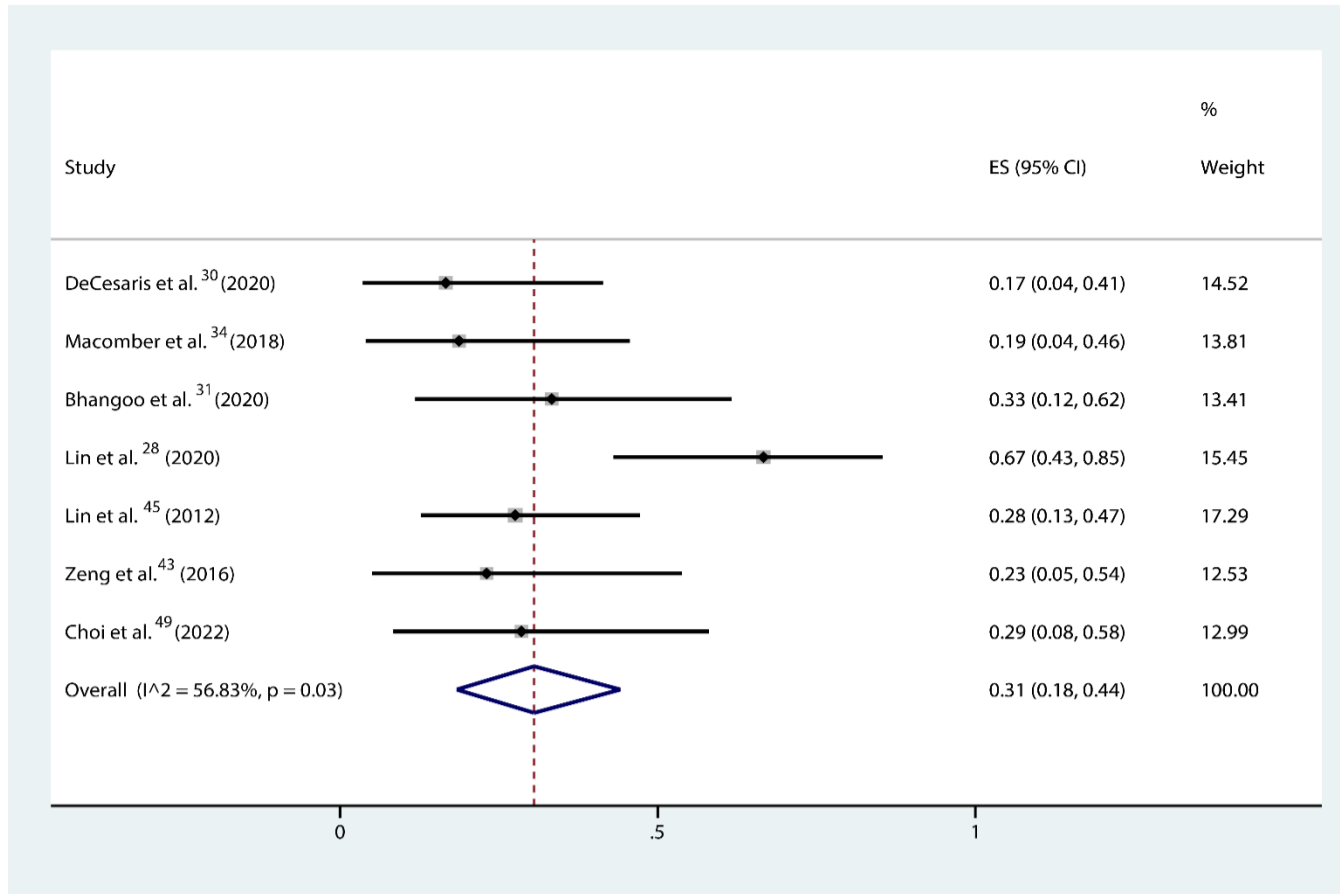
A/B: 2y-OS; C/D: 2y-PFS; A/C: sub-group by treatment modalities (neoadjuvant, racial, or mixed); B/D: sub-group by stage (III-IV < 50% or ≥ 50%).



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



**eFigure 7.** Single-Rate Pooled Analysis of pCR (Proton Therapy)



**eTable 1.** Detailed Comparison Information on OARs Dosimetric and Planning Quality From Proton and Photon Radiotherapy Planning

Reference	Patients	Characteristics	Dose limitations	OARs dose (% diff. between means)	Plans quality
Ribeiro et al. <sup>10</sup> 2021	10 (20)	PBT (IMPT) vs. VMAT (4DCT) PTV: 41.4 Gy/23F Site: L (80%)	-	Lung: *D <sub>mean</sub> ↓: 3.8Gy. Heart: *D <sub>mean</sub> ↓: 9.5Gy.	No SS change
Zhang et al. <sup>11</sup> 2021	25	PBT (PSPT) vs. IMRT/ VMAT (4DCT) PTV: 50.4 Gy/28F Site: -	Lung: D <sub>mean</sub> <20Gy, V <sub>5</sub> <50%, V <sub>10</sub> <40%, V <sub>20</sub> <20%; Heart: D <sub>mean</sub> <20Gy; VB: D <sub>mean</sub> <18.8Gy, V <sub>10</sub> <54.2% (<260 cc), V <sub>20</sub> <44.3% (<225 cc).	# (vs. IMRT) Lung: *D <sub>mean</sub> ↓: 3.0Gy, *V <sub>5, 10</sub> ↓: 25.3%, 12.9%, V <sub>20</sub> ↓: 4.8%. Heart: *D <sub>mean</sub> ↓: 5.6Gy. SC: *D <sub>max</sub> ↓: 2.4Gy. VB: *D <sub>mean</sub> ↓: 4.9Gy, *V <sub>10, 20</sub> ↓: 18.5%, 12.6%. # (vs. VMAT) Lung: *D <sub>mean</sub> ↓: 3.6Gy, *V <sub>5, 10, 20</sub> ↓: 31.7%, 20.4%, 3.7%. Heart: D <sub>mean</sub> ↓: 2.6Gy. SC: D <sub>max</sub> ↑: 4.1Gy. VB: *D <sub>mean</sub> ↓: 2.8Gy, *V <sub>10, 20</sub> ↓: 14.9%, 8.2%.	No SS change
Anakotta et al. <sup>12</sup> 2020	19 (20)	PBT (IMPT) vs. VMAT (4DCT) PTV: 41.4-51Gy/17-28F Site: L (18)	Lung: D <sub>mean</sub> ≤20Gy, V <sub>5</sub> ≤70%, V <sub>20</sub> ≤30%; Heart: D <sub>mean</sub> ≤26Gy.	Lung: *D <sub>mean</sub> ↓: 5.0Gy, *V <sub>5, 20</sub> ↓: 32.6%, 5.6%. Heart: *D <sub>mean</sub> ↓: 11.8Gy, *V <sub>5</sub> ↓: 56.3%. SC: *D <sub>max</sub> ↓: 6.2Gy.	No SS change
Celik et al. <sup>13</sup> 2020	20	PBT (IMPT) vs. VMAT PTV: 41.4Gy/23F Site: L	Lung: D <sub>mean</sub> ≤12Gy, V <sub>20</sub> ≤20%; Heart: D <sub>mean</sub> ≤10Gy, V <sub>30</sub> ≤10%.	Lung: *D <sub>mean</sub> ↓: 5.7Gy, *V <sub>20</sub> ↓: 4.6%. Heart: *D <sub>mean</sub> ↓: 6.2Gy, *V <sub>30</sub> ↓: 1.0%. LV/ LCA/ LAD: *D <sub>mean</sub> ↓: 4.6/ 3.3/ 3.0Gy.	SS HI ↓; no SS CI
Liu et al. <sup>14</sup> 2019	19 vs. 16	PBT (IMPT) vs. VMAT (4DCT) PTV: 41.4-50.4 Gy Site: -	Lung: D <sub>mean</sub> <15Gy, V <sub>5</sub> <60%, V <sub>20</sub> <15%; Heart: D <sub>mean</sub> <26Gy, V <sub>25</sub> <50%, V <sub>40</sub> <30%.	^Lung: *D <sub>mean</sub> ↓: 4.8Gy, *V <sub>5</sub> ↓: 32.5%, V <sub>20</sub> ↓: 1.8%. (med) ^Heart: *D <sub>mean</sub> ↓: 14.3Gy, *V <sub>20</sub> ↓: 35.5%, V <sub>30, 40</sub> ↓: 7.0%, 2.1%. ^SC: D <sub>max</sub> ↑: 2.9Gy.	No SS change
Møller et al. <sup>15</sup> 2019	26	PBT (SFUD) vs. IMRT PTV: 41.4-50Gy/23-25F Site: M/L (5/21)	Lung: D <sub>mean</sub> <19Gy, V <sub>5</sub> <60%, V <sub>20</sub> <35%; Heart: V <sub>25</sub> <40%, V <sub>40</sub> <30%.	#Lung: *D <sub>mean</sub> ↓: 6.6Gy, *V <sub>5, 20</sub> ↓: 41.1%, 8.2%. #Heart: *D <sub>mean</sub> ↓: 7.9Gy, V <sub>25</sub> ↓: 5.7%, V <sub>40</sub> ↑: 0.2%.	No SS change
Hirano et al. <sup>16</sup> 2018	27 (37)	PBT vs. IMRT/ 3D-CRT PTV: 60Gy/30F Site: U/M/ L (5/9/13)	PBT: Lung: V <sub>20</sub> <20%; Heart: D <sub>mean</sub> <26Gy, V <sub>30</sub> <46%. IMRT: Lung: V <sub>20</sub> <30%; Heart: D <sub>mean</sub> <50Gy. 3D-CRT: -	(vs. IMRT) Lung: *D <sub>mean</sub> ↓: 3.6Gy, *V <sub>5, 10, 15, 20</sub> ↓: 19.9%, 8.7%, 5.1%, 6.1%. SC: D <sub>max</sub> ↓: 1.6Gy. Heart: *D <sub>mean</sub> ↑: 8.1Gy, *V <sub>20, 30, 40</sub> ↓: 30.8%, 28.7%, 10.3%. (vs. 3D-CRT) Lung: *D <sub>mean</sub> ↓: 2.4Gy, *V <sub>5, 20</sub> ↓: 7.8%, 5.3%; V <sub>10, 15</sub> ↓: 4.4%, 3.8%. SC: *D <sub>max</sub> ↓: 9.1Gy. Heart: *D <sub>mean</sub> ↓: 13.4Gy, *V <sub>20, 30, 40</sub> ↓: 25.6%, 34.1%, 31.9%.	(vs. IMRT) SS CI ↑; (vs. 3D-CRT) SS CI ↓
Shiraishi et al. <sup>17</sup> 2017	250 vs. 477	PBT (95% PSPT) vs. IMRT (4DCT) PTV: 50.4Gy/28F Site: L (223 vs. 428)	Lung: D <sub>mean</sub> ≤20Gy, V <sub>5</sub> <55%, V <sub>20</sub> ≤35%; Heart: D <sub>mean</sub> <26Gy, V <sub>30</sub> ≤45%.	Heart: *D <sub>mean</sub> ↓: 10.4Gy, *V <sub>5, 10, 20, 30, 40</sub> ↓: 49.6%, 42.4%, 23.0%, 10.8%, 3.5%. LA/ LV: *D <sub>mean</sub> ↓: 4.0/ 9.5Gy; RA/ RV: *D <sub>mean</sub> ↓: 10.0/ 14.8 Gy. LMC/ LAD/ LCX/ RCA: *D <sub>mean</sub> ↓: 16.8/ 11.1/ 3.5/ 15.1 Gy.	No SS change
Warren et al. <sup>18</sup> 2017	21	PBT vs. VMAT PTV: 62.5 Gy/25F Site: M	TV: -	#TV: *D <sub>mean</sub> ↓: 3.3Gy, *V <sub>10, 20</sub> ↓: 4%, 10.8%.	No SS change
Warren et al. <sup>19</sup> 2016	21	PBT vs. VMAT PTV: 62.5 Gy/25F Site: M	Lung: D <sub>mean</sub> <20Gy, V <sub>20</sub> <25%; Heart: D <sub>mean</sub> <25Gy, V <sub>30</sub> <45%.	Lung: *D <sub>mean</sub> ↓: 6.8Gy, *V <sub>20</sub> ↓: 8.8%. Heart: *D <sub>mean</sub> ↓: 8.5Gy.	No SS change
Ling et al. <sup>20</sup> 2014	10	PBT vs. 3DCRT/IMRT PTV: 50.4Gy/28F Site: L	Lung: V <sub>20</sub> <30%; Heart: V <sub>40</sub> <30%.	(vs. IMRT) Lung: *D <sub>mean</sub> ↓: 3.5Gy, *V <sub>5, 10, 15</sub> ↓: 25.5%, 18.4%, 10.6%, V <sub>20, 30, 50</sub> ↓: 0.9%, 0.5%, 0.5%, V <sub>40</sub> ↑: 0.8%. Heart: *D <sub>mean</sub> ↓: 15.9Gy, *V <sub>25, 30, 40, 50</sub> ↓: 30.4%, 21.4%, 9.3%, 9.2%. LAD/ LV/ PC: *D <sub>mean</sub> ↓: 17.2/ 16.4/ 12.5Gy. SC: *D <sub>max</sub> ↓: 25.3Gy. (vs. 3D-CRT) Lung: *D <sub>mean</sub> ↓: 3.4Gy, *V <sub>5, 50</sub> ↓: 12.7%, 2.2%; V <sub>10, 15, 20, 30, 40</sub> ↓: 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> ↓: 14.7/ 13.9/ 11.3Gy.	(vs. IMRT) no SS CI, HI (vs. 3D-CRT) no SS CI, SS HI ↑
Welsh et al. <sup>21</sup> 2011	10	PBT (IMPT) vs. IMRT (4DCT) PTV: 50.4Gy/28F Site: -	-	Lung: *D <sub>mean</sub> ↓: 3.4Gy, *V <sub>5, 10</sub> ↓: 19%, 8%, V <sub>20</sub> ↓: 3%. Heart: *D <sub>mean</sub> ↓: 9.3Gy, *V <sub>10, 20, 30</sub> ↓: 50%, 22%, 8%, V <sub>40, 50</sub> ↓: 2%, 0%. SC: D <sub>max</sub> ↑: 0.1Gy.	-
Zhang et al. <sup>22</sup> 2008	15	PBT (PSPT) vs. IMRT (4DCT) PTV: 50.4 Gy/25F Site: L	-	#Lung: *D <sub>mean</sub> ↓: 3.0Gy, *V <sub>5, 10, 20, 30</sub> ↓: 17.4%, 8.4%, 5.0%, 0.5%. #SC: D <sub>max</sub> ↓: 15.4Gy. #Heart: *V <sub>40</sub> ↓: 8.0%; *V <sub>50</sub> ↑: 0.9%.	SS CI ↑
Mu et al. <sup>23</sup> 2011	10	PBT vs. IMRT PTV: 60Gy/30F Site: U	Lung: V <sub>5</sub> <42%, V <sub>10</sub> <35%; V <sub>20</sub> <20%;	Lung: *D <sub>mean</sub> ↓: 4.8Gy, *V <sub>5, 20</sub> ↓: 31.4%, 6.1%. SC: D <sub>max</sub> ↓: 6.5Gy.	SS CI ↑
Wang et al. <sup>24</sup> 2015	55	PBT (PSPT) vs. IMRT PTV: 50.4Gy/28F Site: -	Lung: D <sub>mean</sub> ≤20Gy, V <sub>20</sub> ≤35%/ 30%; Heart: D <sub>mean</sub> <26Gy, V <sub>30</sub> ≤45%.	Lung: *D <sub>mean</sub> ↓: 2.9Gy, *V <sub>5, 10, 20</sub> ↓: 20.3%, 9.7%, 4.2%. Heart: *V <sub>10, 20, 30</sub> ↓: 32.7%, 13.3%, 2.5%. SC: D <sub>max</sub> ↓: 8.5Gy.	No SS change
Suh et al. <sup>25</sup> 2021	48 vs. 29	PBT vs. 3D-CRT/IMRT (24/5) PTV: 66Gy/33F (med) *Site: L (58% vs. 28%)	-	# ^ (vs. photon) Lung: *D <sub>mean</sub> ↓: 4.8Gy, *V <sub>5, 10, 20, 30</sub> ↓: 26.1%, 14.6%, 3.5%. Heart: *D <sub>mean</sub> ↓: 17.7Gy, *V <sub>5, 10, 20, 30</sub> ↓: 12.7%, 12.7%, 46%, 43.3%.	-
Sumiya et al. <sup>27</sup> 2021	54 vs. 15	PBT vs. 3D-CRT PTV: 56-70Gy/28-35F Site: M+L (80% vs. 67%)	-	WTB: *V <sub>5, 10, 20, 30, 40, 50</sub> ↓: 10.1%, 8.6%, 16.5%, 26.6%, 19%, 5.3%, V <sub>60</sub> ↓: 0.4%.	-
Lin et al. <sup>28</sup> 2020	46 vs. 61	PBT (80% PSPT) vs. IMRT PTV: 50.4Gy/28F	Lung: D <sub>mean</sub> <20Gy, V <sub>5</sub> <60%, V <sub>10</sub> <40%, V <sub>20</sub> <35%;	#Lung: *D <sub>mean</sub> ↓: 3.6Gy, *V <sub>5, 20</sub> ↓: 21.7%, 5.2%. #Heart: *D <sub>mean</sub> ↓: 8.5Gy.	PTV coverage SS ↑



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

Key: All represent as mean ± 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 ≥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 Quality Assessment Using the Newcastle-Ottawa Scale for Non-RCT Studies (Dosimetric Parameters)**

Reference	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that the interest was not present at start of study	Comparability of Cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcome to occur	Adequacy of follow-up of cohorts	Total score
Zhang et al. <sup>11</sup> 2021	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Anakotta et al. <sup>12</sup> 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Celik et al. <sup>13</sup> 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Liu et al. <sup>14</sup> 2019	☆	☆	☆	☆	☆	☆	☆	☆	8
Møller et al. <sup>15</sup> 2019	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Hirano et al. <sup>16</sup> 2018	☆	☆	☆	☆	☆	☆	☆	☆	8
Shiraishi et al. <sup>17</sup> 2017	☆	☆	☆	☆	☆	☆	☆	☆	8
Warren et al. <sup>18</sup> 2017	☆	☆	☆	☆	☆	☆	☆	☆	8
Warren et al. <sup>19</sup> 2016	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Ling et al. <sup>20</sup> 2014	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Welsh et al. <sup>21</sup> 2011	☆	☆	☆	☆	☆	☆	☆	☆	8
Zhang et al. <sup>22</sup> 2008	☆	☆	☆	☆	☆	☆	☆	☆	8
Mu et al. <sup>23</sup> 2011	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Sumiya et al. <sup>27</sup> 2021	☆	☆	☆	☆	-	☆	☆	☆	7
Lin et al. <sup>28</sup> 2020	☆	☆	☆	☆	☆	☆	☆	☆	8
Wang et al. <sup>29</sup> 2020	☆	☆	☆	☆	-	☆	☆	☆	7
Bhangoo et al. <sup>31</sup> 2020	☆	☆	☆	☆	☆	☆	☆	☆	8
Xi et al. <sup>35</sup> 2017	☆	☆	☆	☆	☆	☆	☆	☆	8
Lin et al. <sup>37</sup> 2017	☆	☆	☆	☆	☆	☆	☆	☆	8
Kato et al. <sup>50</sup> 2022	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Zhang et al. <sup>51</sup> 2022	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Cui et al. <sup>52</sup> 2022	☆	☆	☆	☆	☆☆	☆	☆	☆	9

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

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

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

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

**eTable 5. Results of Quality Assessment Using the MINORS (Single-Group Tests)**

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

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

	vs. 3D-CRT	vs. IMRT	vs. VMAT	Overall (Proton vs. Photon)	Egger's test (P value)
<b>Lung</b>					
D <sub>mean</sub> (Gy)	-3.46 (-5.03, -1.88) I <sup>2</sup> = 77%	-4.66 (-5.70, -3.61) I <sup>2</sup> = 88%	-4.41 (-7.14, -1.68) I <sup>2</sup> = 96%	-4.42 (-5.38, -3.47) I <sup>2</sup> = 93%	0.959
V <sub>5</sub> (%)	-8.83 (-13.55, -4.11) I <sup>2</sup> = 0%	-26.89 (-32.19, -21.58) I <sup>2</sup> = 86%	-25.93 (-47.42, -4.45) I <sup>2</sup> = 98%	-24.81 (-31.40, -18.21) I <sup>2</sup> = 95%	0.199
V <sub>10</sub> (%)	-5.35 (-9.38, -1.32) I <sup>2</sup> = 0%	-12.87 (-17.91, -7.83) I <sup>2</sup> = 83%	-17.51 (-26.57, -8.45) I <sup>2</sup> = 79%	-12.92 (-16.84, -9.00) I <sup>2</sup> = 82%	0.359
V <sub>20</sub> (%)	-5.48 (-8.18, -2.78) I <sup>2</sup> = 0%	-7.16 (-9.77, -4.55) I <sup>2</sup> = 89%	-5.55 (-7.71, -3.38) I <sup>2</sup> = 64%	-6.52 (-8.24, -4.79) I <sup>2</sup> = 84%	0.511
V <sub>30</sub> (%)	- I <sup>2</sup> = 0%	-3.56 (-9.24, 2.12) I <sup>2</sup> = 95%	- I <sup>2</sup> = 0%	-3.05 (-5.86, -0.25) I <sup>2</sup> = 89%	*
V <sub>40</sub> (%)	- I <sup>2</sup> = 0%	- I <sup>2</sup> = 0%	- I <sup>2</sup> = 0%	-0.26 (-0.87, 0.34) I <sup>2</sup> = 0%	*
<b>Heart</b>					
D <sub>mean</sub> (Gy)	-15.08 (-16.36, -13.80) I <sup>2</sup> = 0%	-8.74 (-10.53, -6.94) I <sup>2</sup> = 90%	-8.86 (-12.02, -5.69) I <sup>2</sup> = 89%	-9.52 (-11.11, -7.94) I <sup>2</sup> = 92%	0.588
V <sub>5</sub> (%)	/ I <sup>2</sup> = 0%	-45.29 (-51.22, -39.37) I <sup>2</sup> = 81%	-42.51 (-70.90, -14.13) I <sup>2</sup> = 92%	-45.06 (-51.18, -38.94) I <sup>2</sup> = 82%	*
V <sub>10</sub> (%)	/ I <sup>2</sup> = 0%	-42.36 (-49.92, -34.79) I <sup>2</sup> = 66%	- I <sup>2</sup> = 0%	-39.52 (-47.45, -31.60) I <sup>2</sup> = 72%	*
V <sub>20</sub> (%)	- I <sup>2</sup> = 0%	-25.36 (-30.17, -20.55) I <sup>2</sup> = 41%	- I <sup>2</sup> = 0%	-26.60 (-31.90, -22.12) I <sup>2</sup> = 43%	*
V <sub>30</sub> (%)	-22.75 (-44.70, -0.81) I <sup>2</sup> = 92%	-13.07 (-16.67, -9.48) I <sup>2</sup> = 85%	-10.51 (-22.16, 114) I <sup>2</sup> = 93%	-13.89 (-17.84, -9.95) I <sup>2</sup> = 93%	<0.001
V <sub>40</sub> (%)	-20.54 (-42.39, 1.31) I <sup>2</sup> = 93%	-5.17 (-7.92, -2.43) I <sup>2</sup> = 82%	-9.23 (-32.05, 13.59) I <sup>2</sup> = 95%	-7.44 (-10.66, -4.22) I <sup>2</sup> = 89%	<0.001
V <sub>50</sub> (%)	- I <sup>2</sup> = 0%	-1.92 (-7.57, 3.74) I <sup>2</sup> = 82%	/ I <sup>2</sup> = 0%	-5.28 (-12.27, 1.70) I <sup>2</sup> = 89%	*
LV-D <sub>mean</sub> (Gy)	- I <sup>2</sup> = 0%	-12.43 (-19.11, -5.75) I <sup>2</sup> = 84%	- I <sup>2</sup> = 0%	-10.20 (-14.32, -6.08) I <sup>2</sup> = 95%	*
LAD-D <sub>mean</sub> (Gy)	- I <sup>2</sup> = 0%	-13.88 (-19.84, -7.93) I <sup>2</sup> = 90%	- I <sup>2</sup> = 0%	-11.24 (-17.31, -5.61) I <sup>2</sup> = 99%	*
<b>BM</b>					
D <sub>mean</sub> (Gy)	/ I <sup>2</sup> = 0%	- I <sup>2</sup> = 0%	-3.00 (-5.25, -0.75) I <sup>2</sup> = 28%	-2.89 (-4.46, -1.32) I <sup>2</sup> = 0%	*
V <sub>10</sub> (%)	- I <sup>2</sup> = 0%	- I <sup>2</sup> = 0%	-11.22 (-16.34, -6.10) I <sup>2</sup> = 0%	-10.21 (-13.99, -6.42) I <sup>2</sup> = 0%	*
V <sub>20</sub> (%)	- I <sup>2</sup> = 0%	- I <sup>2</sup> = 0%	-9.68 (-19.28, -0.08) I <sup>2</sup> = 77%	-10.33 (-16.20, -4.47) I <sup>2</sup> = 69%	*
<b>SC</b>					
D <sub>max</sub> (Gy)	-13.52 (-23.56, -3.48) I <sup>2</sup> = 81%	-7.14 (-10.95, -3.34) I <sup>2</sup> = 92%	-3.86 (-9.39, 1.67) I <sup>2</sup> = 89%	-6.93 (-9.73, -4.13) I <sup>2</sup> = 91%	0.097

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<sub>mean</sub>: mean dose; V<sub>x</sub>: percentage of volume receiving ≥x Gy; LV: left ventricle; LAD: left anterior descending artery; BM: bone marrow; SC: spinal cord; Heart-V<sub>30</sub>, V<sub>40</sub> 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.

**eTable 7.** Pooled Analysis of the Incidence of Toxic Effects in the Proton and Photon Therapy Group (Described as OR)

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

**eTable 8.** Single-Rate Pooled Analysis for the Incidence of Toxic Effects in Proton Therapy

	Acute	Late	Unknown	Total
<b>G2+</b>				
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 <sup>2</sup> = 68.7%		^	I <sup>2</sup> = 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 <sup>2</sup> = 91.5%	I <sup>2</sup> = 0%	^	I <sup>2</sup> = 83.4%
PE	/	0.03 (95%CI: 0.00, 0.08)	-	0.04 (95%CI: 0.02, 0.07)
		^		I <sup>2</sup> = 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)
	^	I <sup>2</sup> = 57.8%		I <sup>2</sup> = 62.7%
<b>G3+</b>				
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 <sup>2</sup> = 63.6%		^	I <sup>2</sup> = 57.1%
<b>G4+</b>				
lymphocytopenia	0.17 (95%CI: 0.07, 0.30)	/	/	0.17 (95%CI: 0.07, 0.30)
	I <sup>2</sup> = 93.8%			I <sup>2</sup> = 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.