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Comparison of Deep Inspiration Breath Hold Versus Free Breathing in Radiotherapy for Left Sided Breast Cancer

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Objectives: Modern breast cancer techniques, such as the deep inspiration breath-hold (DIBH) technique has been applied for left-sided breast cancer. Whether the DIBH regimen is the optimal solution for left-sided breast cancer remains unclear. This meta-analysis aims to elucidate the differences of DIBH and free-breathing (FB) for patients receiving radiotherapy for left-sided breast cancer and provide a practical reference for clinical practice.

Methods: Relevant research available on PubMed, Embase, Cochrane Library, and the Web of Science published before November 30, 2021 was independently and systematically examined by two investigators. Data were extracted from eligible studies for assessing their qualities and calculating the standardized mean difference (SMD) and 95% confidence intervals (CIs) using Review Manager software 5.4 (RevMan 5.4).

Results: Forty-one studies with a total of 3599 left-sided breast cancer patients were included in the meta-analysis. Compared with FB, DIBH reduced heart dose (D_{mean}, D_{max}, V30, V10, V5), left anterior descending branch (LAD) dose (D_{mean}, D_{max}), ipsilateral lung dose (D_{mean}, V20, V10, V5), and heart volume significantly. Lung volume increased greatly, and a statistically significant difference. For contralateral breast mean dose, DIBH has no obvious advantage over FB. The funnel plot suggested this study has no significant publication bias.

Conclusions: Although DIBH has no obvious advantage over FB in contralateral breast mean dose, it can significantly reduce heart dose, LAD dose, ipsilateral lung dose, and heart volume. Conversely, it can remarkably increase the ipsilateral lung volume. This study suggests that soon DIBH could be more widely utilized in clinical practice because of its excellent dosimetric performance.

Keywords: left sided breast cancer, radiotherapy, free breathing, deep inspiration breath hold, meta-analysis

INTRODUCTION

Breast cancer is a significant global public health problem and the leading cause of cancer mortality in women (1). Adjuvant radiation therapy has a major role managing this disease, reducing the risk of local recurrence and breast cancer-specific mortality (2). It is certain that radiotherapy is an effective way to treat breast cancer, and significantly prolongs the survival time. However, breast cancer radiation therapy is also associated with higher cardiac and pulmonary toxicity [e.g., radiation-related heart disease (RRHD) (3) and radiation pneumonia (RP) (4)] with an increased risk of secondary cancer (3, 5–9). Darby et al. showed the risk of major coronary events induced by radiation increased linearly with the mean heart dose (MHD) by 7.4% per gray, with no threshold dose (3). Clarke et al. compared a group of irradiated patients with non-irradiated patients and found a significant increase in mortality rate, mainly for heart disease and lung cancer with a rate ratio of 1.27 and 1.78, respectively (2).

Therefore, with patients receiving radiotherapy for breast cancer substantial efforts have been made to develop techniques that reduce heart and lung dose, such as Deep inspiration breath-hold (DIBH). This simple technique reduces cardiac exposure by lung expansion which physically displaces the heart out of the treatment field. There are several approaches for performing DIBH, in particular active breath control, external infrared box marker, and optical surface monitor (10). Studies have demonstrated that DIBH, for left-sided breast cancer patients, can reduce the cardiac dose compared with free-breathing (FB) (5, 9, 11–13). It is noteworthy that the technique has high repeatability and stability in the whole treatment process (14).

Although many studies show DIBH technology is correlated to heart dose, LAD dose, ipsilateral lung dose, contralateral breast dose, heart volume, and ipsilateral lung volume, we have reached an understanding that DIBH is critical and superior to free-breathing (FB) in radiotherapy for left-sided breast cancer. However, there are many small sample studies, which gives a lack confidence. Therefore, we searched all of the controlled studies of DIBH and FB in radiotherapy of the left breast and conducted this meta-analysis. It is noteworthy that the research groups with different radiotherapy techniques (3D-CRT, IMRT, or VMAT), postures (supine or prone position), and prescribed dose schemes (CF or HF) in the same study were included in this meta-analysis.

METHODS

Search Strategy

Using a combination of medical subject heading (MeSH) terms and/or free text words such as, “breast cancer”, “radiotherapy” and “deep inspiration breath-hold or DIBH”, we thoroughly searched four medical databases including PubMed, Embase, Cochrane library, and Web of Science for relevant studies published before November 30, 2021. There was no limitation on the language of published studies. Furthermore, references of selected studies were manually reviewed, and literature searching and screening were independently performed by two investigators. Disagreement was resolved through discussion with a third investigator.

Inclusion Criteria

All studies included were following the principles of PICOS (Participants, Intervention, Comparison and Outcomes, Study design). Inclusion criteria were as follows: (1) Participants [P]: Patients were pathologically diagnosed with left-sided breast cancer without distant metastasis. (2) Intervention [I]: Patients in the experimental group received a DIBH regimen. (3) Comparison [C]: Free-breathing (FB) regimen was the intervention in the control group. (4) Outcomes [O]: The outcomes included dosimetric indicators of heart, left anterior descending artery, ipsilateral lung, and contralateral breast: the mean dose (D_{mean}), the maximum dose (D_{max}), and the percentage of the organ volume receiving at least 5 Gy (V5), 10 Gy (V10), 20 Gy (V20), 25 Gy (V25) and 30 Gy (V30). (5) Study design [S]: randomized controlled trials (RCTs) and observational studies, including cohort and case-control studies. It should be noted that trials with different fractionation regimens and prescribed doses were included in this study.

Exclusion Criteria

Articles satisfying any of the following items were excluded: (1) Reviews, case reports, letters, and abstracts; (2) Low research quality or having a high risk of bias; (3) Lacking available data that could be pooled.

Data Extraction

The following information was independently extracted from the included studies by two researchers (Mr. Yang and Mr. Teng): First author, year of publication, country, study design, age, DIBH type, clinical tumor stage, sample size, detailed treatment plan, and outcomes of the various subgroups. Dispute regarding data extraction was arbitrated by a third investigator (Mr. Tang).

Quality Assessment

To assess the risk of bias in nonrandomized studies Newcastle-Ottawa Scale (NOS) (15) was introduced, involving three perspectives: Selection, comparability, and outcome of the studies. Using a 0-9 scale, 4 points were graded for selection, 2 for comparability, and 3 for outcomes. Studies with 6 points or higher were considered high quality (16).

Statistical Analysis

The pooled statistics were performed using RevMan software version 5.4 (Cochrane Collaboration, Oxford, UK). Standardized mean difference (SMD) and 95% CI were selected as the effect indicator to analyze measurement data. Heterogeneity was evaluated between trials through the Cochrane Q test and the I^2 statistic, which quantified the proportion of total variation caused by heterogeneity instead of chance (17). If the P-value of the Q test was >0.10 and $I^2 < 50\%$, a fixed-effects model was used for data with non-significant heterogeneity. Otherwise, a random-effects model was used for data with significant heterogeneity (18, 19). Furthermore, the sensitivity analysis was also applied to examine the potential influence of an individual study on the overall assessment, which involved removing one study each time and pooling the remaining trials. A funnel plot was used to understand the bias of the literature publication. If the points in the funnel plot are symmetrically distributed on both sides of the middle dashed line and concentrate in the center, the possibility of publication bias is low. If not, the possibility of publication bias could be high.

RESULTS

Study Selection

Initially, after excluding 236 duplicates, 232 articles were retrieved through preliminary searches in PubMed, Embase, the Cochrane Library, and Web of Science. Then, 62 unqualified articles were eliminated through reviewing titles and abstracts. After a full-text reading, 41 qualified articles were assessed for design and quality (5, 7, 20, 13, 21–57). The detailed process of the study selection is shown in **Figure 1**.

Study Characteristics

Finally, 41 studies (5, 7, 13, 20–57) totaling 3599 left-sided breast cancer patients were included in our meta-analysis. All articles included were retrospective studies and identified as high quality by the Newcastle–Ottawa Scale (15). **Table 1** summarizes the baselines information of the 41 included studies. Each group of data shall be counted independently when multiple groups of data are in the same study.

Heart Dose

Heart dose data (D_{mean}, D_{max}, V30, V10, and V5) were extracted from 38 articles which studied 3507 patients. The random-effects model was applied due to the significant between-study heterogeneity ($I^2 \geq 50\%$, P ≤ 0.10). The pooled results showed there was a difference between the DIBH group and FB group. By combining the results with clinical information from the

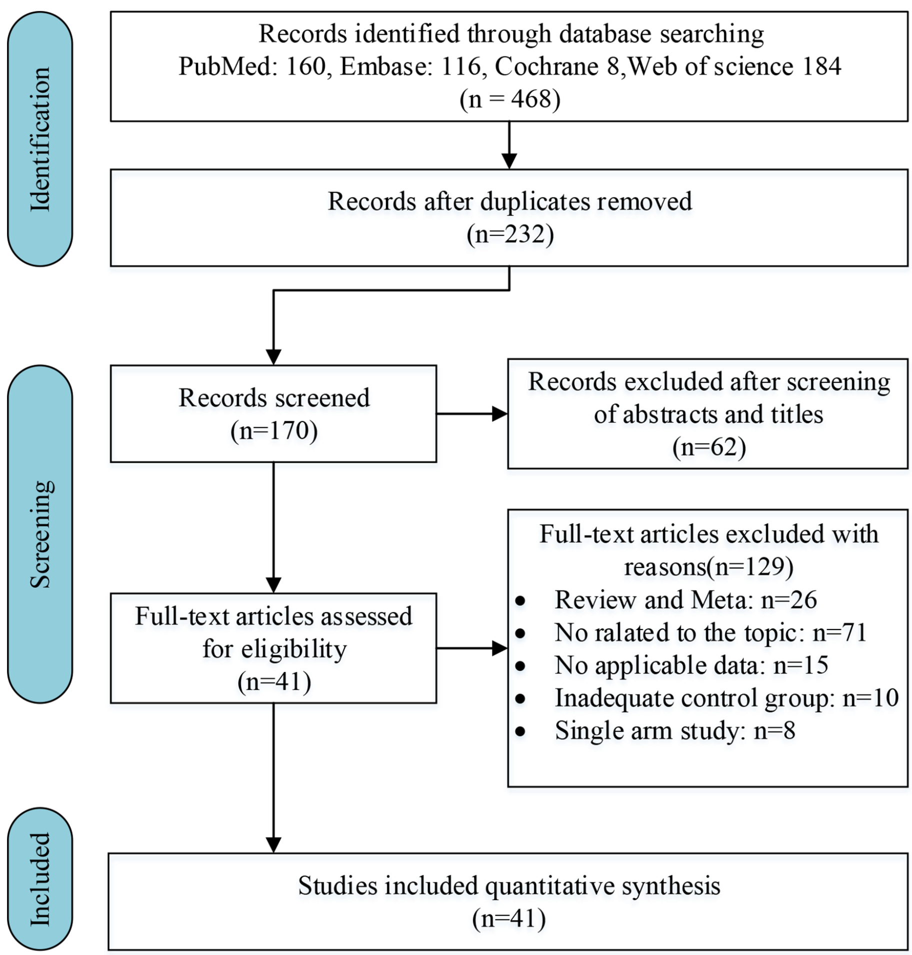


FIGURE 1 | Flow chart of the search process for the meta-analysis.

TABLE 1 | Characteristics of the studies included in the meta-analysis.

First author (year of publication)	Total Patients (DIBH/FB)	Clinical stage	Median age (years)	Prescription dose(Gy)/Fractions(F)	DIBH types	Study type	NOS score
Angela 2017 (20)	64 (32/32)	NA	NA	50 Gy/25 F	RPM	Retrospective	6
Bruzzaniti 2013 (CF) (21)	16 (8/8)	NA	51	50 Gy/25 F	RPM	Retrospective	7
Bruzzaniti 2013 (HF) (21)	16 (8/8)	NA	51	34 Gy/10 F	RPM	Retrospective	7
Chatterjee 2018 (22)	70 (50/20)	NA	NA	40 Gy/15 F	RPM	Retrospective	6
Chi. F. 2015 (23)	62 (31/31)	I or II	39.5	50 Gy/25 F	ABC	Retrospective	8
Christina 2021 (24)	194 (97/97)	NA	54	40.05-50.4 Gy/15 -28 F	RPM	Retrospective	7
Comsa 2014 (25)	60 (30/30)	NA	<50	50 Gy/25 f	ABC	Retrospective	6
Dincoglan 2013 (26)	54 (27/27)	NA	<65	50 Gy/25 f	ABC	Retrospective	7
Dolezel 2021 (27)	200 (100/100)	cT1-3N0-2	59	48.6 Gy/27 f	NA	Retrospective	7
Eldredge 2015 (28)	172 (86/86)	T1–3N0–3M0	52	50 Gy/25 f	ABC	Retrospective	9
Ferini 2021 (29)	232 (116/116)	I-II	56	40.5-50 Gy/15-25 f	RPM	Retrospective	8
Goyal 2020 (30) (prone position)	28 (14/14)	NA	>18	40-42.6 Gy/15-16 f	RPM	Retrospective	7
Hammadi 2018 (31)	108 (54/54)	NA	41	50 Gy/25 f	NA	Retrospective	6
Hepp 2015 (32)	40 (20/20)	pTis–pT1 pN0	NA	50 Gy/25 f	Catalyst	Retrospective	7
Jensen 2017 (33)	44 (22/22)	pT1-2N0M0, ductal carcinoma	58	50 Gy/25 f	laser-based DIBH system	Retrospective	7
Jiheon 2020 (34)	150 (75/75)	Invasive breast cancer or ductal carcinoma	NA	40-42.5 Gy/15-16 f	Medspira Breath-Hold	Retrospective	7
Kunheri 2017 (35)	90 (45/45)	I–IIIA	45.2	40 Gy/15 f	ABC	Retrospective	8
Lastrucci 2017 (36)	46 (23/23)	NA	NA	50 Gy/25 f	Medspira Breath-Hold	Retrospective	7
Lawler 2017 (37)	56 (28/28)	NA	57.39	40.05–50 Gy/15–25 f	RPM	Retrospective	7
Lee 2013 (38)	50 (25/25)	≤T2 and ≤N1a	29	50.4 Gy/28f	Abches	Retrospective	8
Lin 2019 (39)	184 (63/121)	Tis, I, or II	51.53	50 Gy/25 f	ABC	Retrospective	8
Liuwei 2021 (40)	22 (11/11)	NA	NA	42.4 Gy/16f	NA	Retrospective	6
Misra 2021 (41)	60 (30/30)	I-III	50	40 Gy/15f	RPM	Retrospective	9
Mohamad 2017 (42)	44 (22/22)	NA	NA	50 Gy/25 f	ABC	Retrospective	6
Nissen 2013 (43)	227 (144/83)	NA	55.5 (DIBH) 64 (FB)	50 Gy/25 f	ABC	Retrospective	9
Pham 2016 (44) (IMRT Group)	30 (15/15)	NA	NA	50 Gy/25 f	RPM	Retrospective	6
First author (year of publication)	Total Patients (DIBH/FB)	Clinical stage	Median age (years)	Prescription dose(Gy)/Fractions(F)	DIBH types	Study type	NOS score
Pham 2016 (44) (VMAT Group)	30 (15/15)	NA	NA	50 Gy/25 f	RPM	Retrospective	6
Rochet 2015 (45)	70 (35/35)	Tis-T3N+M0	51	42.4–50-50.4 Gy/16–25-28 f	AlignRT	Retrospective	7
Saini 2018 (46)	66 (33/33)	T1-2N0	NA	42.56 Gy/16 f	DIBH (other)	Retrospective	7
Saini 2019 (7) (prone position)	50 (25/25)	T1-2N0	NA	42.56 Gy/16 f	DIBH (other)	Retrospective	7
Saini 2019 (7) (supine position)	50 (25/25)	T1-2N0	NA	42.56 Gy/16 f	DIBH (other)	Retrospective	7
Sakka 2017 (47) (IMRT Group)	40 (20/20)	NA	<70	50.4 Gy/28 f	RPM	Retrospective	7
Sakka 2017 (47) (VMAT Group)	40 (20/20)	NA	<70	50.4 Gy/28 f	RPM	Retrospective	7
Sakyanun 2020 (48)	50 (25/25)	NA	NA	50 Gy/25 f	RPM	Retrospective	6

(Continued)

TABLE 1 | Continued

First author (year of publication)	Total Patients (DIBH/FB)	Clinical stage	Median age (years)	Prescription dose(Gy)/Fractions(F)	DIBH types	Study type	NOS score
Schönecker 2016 (49)	18 (9/9)	NA	46.9	50 Gy/25 f	Catalyst/Sentinel	Retrospective	7
Shim 2012 (50)	20 (10/10)	T1N0, T2N0,T2N1	44	50 Gy/25 f	NA	Retrospective	6
Simonetto 2019 (51)	198 (89/89)	Tis-T4	57	40-50 Gy/15-25 f	Catalyst/Sentinel	Retrospective	9
Stranzl 2009 (52)	22 (11/11)	NA	51	NA	RPM	Retrospective	6
Sunmin 2021 (53)	30 (15/15)	T1-2N0	54	50 Gy/25 f	RPM	Retrospective	9
Tanguturi 2015 (54)	148 (110/38)	All stages	58/49.5	50 Gy/25 f	AlignRT	Retrospective	8
Vikström 2011 (55)	34 (17/17)	NA	60	50 Gy/25 f	RPM	Retrospective	6
Wang 2012 (13)	106 (53/53)	NA	52	42.4–50 Gy/16–25 f	ABC	Retrospective	8
Wiant 2015 (56)	50 (25/25)	NA	NA	50.4 Gy/28 f	Philips Bellows system	Retrospective	7
Yamauchi 2020 (5)	170 (85/85)	NA	49.3	50 Gy/25 f	RPM	Retrospective	7
Zhao-Feng 2018 (57) (3D-CRT Group)	44 (22/22)	NA	48	50 Gy/25 f	RPM	Retrospective	7
Zhao-Feng 2018 (57) (IMRT Group)	44 (22/22)	NA	48	50 Gy/25 f	RPM	Retrospective	7

DIBH, deep inspiration breath hold; FB, free breathing; NOS, Newcastle–Ottawa Scale; CF, conventional fractionation; HF, Hypofractionation; ABC, active breathing coordinator; RPM, real-time position management; AlignRT, a realtime surfacetracking system; VMAT, volumetric modulated arc therapy; IMRT, intensity-modulated radiation therapy; 3D-CRT, 3-dimensional conformal radiotherapy; NA, not available.

included studies, it was indicated that DIBH technology can decrease heart doses more effectively than the FB group. The results are presented in **Figures 2** and **3**, D_{mean} (SMD = -1.28, 95% CI: -1.42 - 1.13, P<0.01), D_{max} (SMD = -1.86, 95% CI: -2.26 ~ -1.46, P<0.01), V30 (SMD = -1.23, 95% CI: -1.49 ~ 0.97 P<0.01), V10 (SMD = - 1.40, 95% CI: -1.65 ~ -1.15, P<0.01), V5 (SMD = -1.58, 95% CI: -2.05 ~ -1.12, P<0.01).

LAD Dose

Twenty-seven studies involving 2146 patients were eligible for analyzing the LAD dose (D_{mean} and D_{max}). Significant heterogeneity was identified (I^2≥50%, P ≤ 0.10) and as a result, a random-effects model was employed to calculate the pooled data. The data demonstrated that the LAD dose (D_{mean} and D_{max}) of the DIBH group was significantly lower than that of the FB group (D_{mean}: SMD = -1.35, 95% CI: -1.57 ~ -1.13, P<0.01; D_{max}: SMD = -1.26, 95% CI: -1.61 ~ -0.90, P<0.01) (**Figure 4**).

Ipsilateral Lung Dose

Ipsilateral lung dosimetric indicators (D_{mean}, V20, V10, and V5) were extracted from 33 studies with 2768 patients. The heterogeneity test showed statistically significant differences among the studies (I^2 ≥ 50%, P ≤ 0.10), and therefore, a random-effects model was introduced. Compared to the FB group, left-sided breast cancer patients could benefit more from DIBH technology. The results are presented in **Figures 5** and **6**, D_{mean} (SMD = - 0.55, 95% CI: -0.73 ~ -0.37, P<0.01), V20 (SMD = -2.62, 95% CI: -3.37 ~ -1.87 P<0.01), V10 (SMD = -2.71, 95% CI: -3.71 ~ -1.72, P<0.01), V5 (SMD = - 2.08, 95% CI: -3.11 ~ -1.04, P<0.01).

Contralateral Breast Mean Dose

Eight studies, with 578 left-sided breast cancer patients in total, were included in this analysis. During the analysis, we found no significant between-study heterogeneity (I^2 = 0%; p = 0.53), and a fixed-effects model was used. The combined analysis showed that there was no significant difference in contralateral breast mean dose between the two groups and there was no statistical significance (SMD = -0.19, 95% CI: -0.36 ~ -0.03, P=0.02) (**Figure 7**).

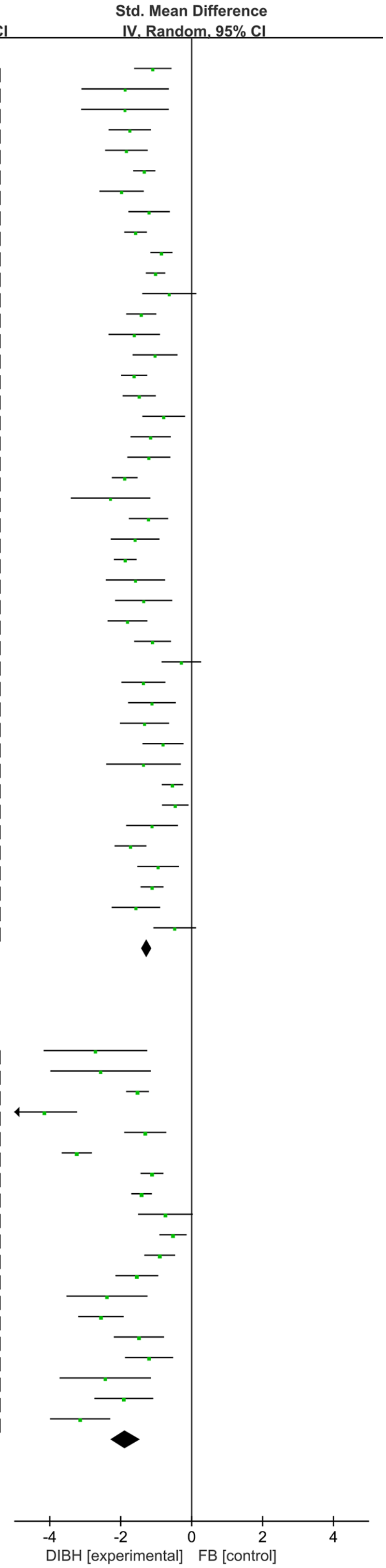
Heart Volume

Heart volume was reported in eleven studies with a total of 832 patients. The fixed-effects model was applied due to no significant between-study heterogeneity (I^2 = 32%; p = 0.14). In comparison with the FB group, the application of DIBH technology makes cardiac volume compression in patients with left-sided breast cancer. (SMD = -0.32, 95% CI: -0.46 ~ -0.18, P<0.01) (**Figure 8**).

Ipsilateral Lung Volume

Fifteen studies involving 1599 left-sided breast cancer patients were eligible for analysis. The fixed-effects model was conducted for no significant between-study heterogeneity (I^2 = 0%; p = 0.55). Meta-analysis showed that DIBH technology significantly increased the ipsilateral lung volume (SMD = 2.35, 95% CI: 2.22 ~ -2.48, P<0.01) (**Figure 9**).

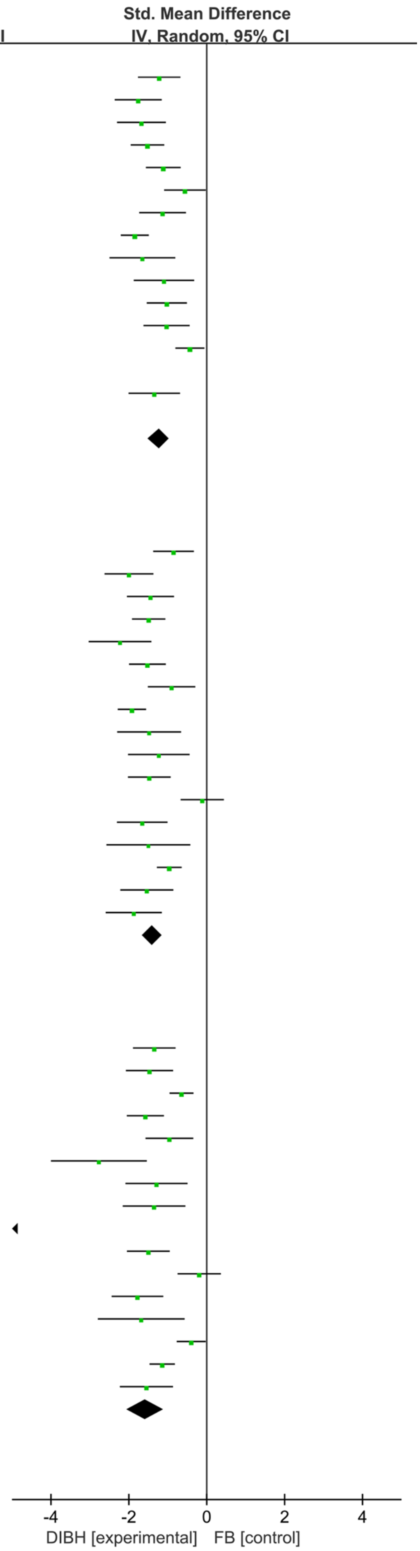
Study or Subgroup	DIBH Mean	DIBH SD	DIBH Total	FB Mean	FB SD	FB Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Heart Dmean (cGy)								
Angela 2017	106.2	40.8	32	190.7	99.7	32	2.5%	-1.10 [-1.62, -0.57]
Bruzzaniti 2013(CF)	124	10	8	168	29.75	8	1.0%	-1.87 [-3.11, -0.64]
Bruzzaniti 2013(HF)	84	6.75	8	114	20.25	8	1.0%	-1.88 [-3.11, -0.65]
Chatterjee 2018	170.9	80.1	50	371.6	172.9	20	2.3%	-1.74 [-2.34, -1.14]
Chi. F. 2015	156.8	46.1	31	282.3	83.4	31	2.3%	-1.84 [-2.44, -1.24]
Christina 2021	300	140	97	580	260	97	3.2%	-1.34 [-1.65, -1.02]
Comsa 2014	209	57	30	448	159	30	2.2%	-1.98 [-2.60, -1.35]
Dincoglan 2013	401	194.8	27	676.8	254	27	2.3%	-1.20 [-1.78, -0.62]
Dolezel 2021	121	27	100	322	177	100	3.1%	-1.58 [-1.90, -1.26]
Eldredge 2015	90	132.9	86	270	265.8	86	3.2%	-0.85 [-1.17, -0.54]
Ferini 2021	132	60	116	252	155	116	3.3%	-1.02 [-1.29, -0.74]
Goyal 2020 (prone position)	71.86	11.43	14	93.17	44.96	14	1.8%	-0.63 [-1.39, 0.13]
Hammadi 2018	320	140	54	610	250	54	2.8%	-1.42 [-1.84, -1.00]
Hepp 2015	190	40	20	360	140	20	1.9%	-1.62 [-2.34, -0.89]
Jensen 2017	200	90	22	300	100	22	2.2%	-1.03 [-1.66, -0.40]
Jiheon 2020	130	50	75	280	120	75	3.0%	-1.62 [-1.99, -1.25]
Kunheri 2017	159.24	72.5	45	308.55	121.54	45	2.7%	-1.48 [-1.95, -1.01]
Lastrucci 2017	120	110	23	230	160	23	2.3%	-0.79 [-1.39, -0.19]
Lawler 2017	122.4	34.4	28	181.7	62.7	28	2.3%	-1.16 [-1.73, -0.59]
Lee 2013	252	133.3	25	453	189.5	25	2.2%	-1.21 [-1.81, -0.60]
Lin 2019	299.3	183.7	63	797.8	295.8	121	3.0%	-1.89 [-2.25, -1.53]
Liuwei 2021	88	15	11	152	35	11	1.1%	-2.29 [-3.41, -1.17]
Misra 2021	105	36	30	192	93	30	2.4%	-1.22 [-1.77, -0.66]
Mohamad 2017	222.7	102.8	22	578.4	292.4	22	2.0%	-1.59 [-2.28, -0.91]
Nissen 2013	269	137.3	144	518	124	83	3.1%	-1.87 [-2.19, -1.55]
Pham 2016 (IMRT Group)	500	240	15	970	330	15	1.7%	-1.58 [-2.42, -0.75]
Pham 2016 (VMAT Group)	570	140	15	810	200	15	1.7%	-1.35 [-2.16, -0.55]
Rochet 2015	90	30	35	250	120	35	2.4%	-1.81 [-2.37, -1.25]
Saini 2018	108	38.52	33	192	99.26	33	2.5%	-1.10 [-1.62, -0.58]
Saini 2019(prone position)	77	27.41	25	85	26.67	25	2.4%	-0.29 [-0.85, 0.27]
Saini 2019(supine position)	97	40.74	25	188	83.7	25	2.2%	-1.36 [-1.98, -0.74]
Sakka 2017 (IMRT Group)	296	61	20	371	70	20	2.1%	-1.12 [-1.79, -0.45]
Sakka 2017 (VMAT Group)	403	74	20	530	110	20	2.0%	-1.33 [-2.02, -0.64]
Sakyanun 2020	295	230	25	538	350	25	2.3%	-0.81 [-1.39, -0.23]
Schönecker 2016	131	15	9	273	140	9	1.2%	-1.36 [-2.41, -0.31]
Simonetto 2019	150	125.6	89	250	226.5	89	3.2%	-0.54 [-0.84, -0.24]
Tanguturi 2015	137.6	245.2	110	255.7	280	38	3.0%	-0.46 [-0.83, -0.09]
Vikström 2011	170	90	17	370	230	17	1.9%	-1.12 [-1.85, -0.39]
Wang 2012	131.7	37.58	53	317.4	146.4	53	2.7%	-1.72 [-2.17, -1.28]
Wiant 2015	140	50	25	300	230	25	2.3%	-0.95 [-1.53, -0.36]
Yamauchi 2020	75.2	39.9	85	156.2	94	85	3.1%	-1.12 [-1.44, -0.79]
Zhao-Feng 2018 (3D-CRT Group)	134	43	22	289	130	22	2.0%	-1.57 [-2.26, -0.89]
Zhao-Feng 2018 (IMRT Group)	118	26	22	196	225	22	2.3%	-0.48 [-1.08, 0.12]
Subtotal (95% CI)			**1806**			**1701**	**100.0%**	**-1.28 [-1.42, -1.13]**
Heterogeneity: Tau² = 0.15; Chi² = 140.35, df = 42 (P < 0.00001); I² = 70%								
Test for overall effect: Z = 17.34 (P < 0.00001)								
1.1.2 Heart Dmax (cGy)								
Bruzzaniti 2013(CF)	500	200	8	2,919	1,175	8	3.5%	-2.71 [-4.17, -1.25]
Bruzzaniti 2013(HF)	385	175	8	2,475	1,075	8	3.6%	-2.57 [-3.98, -1.15]
Christina 2021	2,730	1,260	97	4,390	870	97	6.2%	-1.53 [-1.85, -1.21]
Comsa 2014	1,020	602	30	4,190	879	30	4.8%	-4.15 [-5.07, -3.23]
Dincoglan 2013	4,024	1,118	27	5,125	353	27	5.7%	-1.31 [-1.90, -0.72]
Dolezel 2021	1,466	1,234	100	4,988	907	100	6.0%	-3.24 [-3.66, -2.82]
Eldredge 2015	2,790	2,425	86	5,040	1,462	86	6.2%	-1.12 [-1.44, -0.80]
Ferini 2021	2,017	1,523	116	3,909	1,116	116	6.3%	-1.41 [-1.70, -1.12]
Goyal 2020 (prone position)	718.69	688.47	14	1,570.29	1,424.78	14	5.2%	-0.74 [-1.51, 0.03]
Hammadi 2018	4,850	680	54	5,110	140	54	6.1%	-0.53 [-0.91, -0.14]
Kunheri 2017	3,416.37	763.73	45	3,919.57	181.84	45	6.0%	-0.90 [-1.33, -0.46]
Lawler 2017	2,738.9	1,239.3	28	4,181	396.3	28	5.7%	-1.55 [-2.15, -0.94]
Liuwei 2021	1,380	842	11	2,933	273	11	4.3%	-2.39 [-3.53, -1.24]
Rochet 2015	2,440	1,420	35	5,250	590	35	5.6%	-2.56 [-3.20, -1.92]
Sakka 2017 (IMRT Group)	2,344	1,243	20	3,895	740	20	5.4%	-1.49 [-2.19, -0.78]
Sakka 2017 (VMAT Group)	2,090	682	20	2,982	773	20	5.5%	-1.20 [-1.88, -0.52]
Schönecker 2016	1,974	1,552	9	4,790	139	9	3.9%	-2.43 [-3.72, -1.14]
Vikström 2011	2,450	1,680	17	4,790	180	17	5.1%	-1.91 [-2.74, -1.08]
Wiant 2015	2,050	930	25	4,720	730	25	5.0%	-3.14 [-3.99, -2.30]
Subtotal (95% CI)			**750**			**750**	**100.0%**	**-1.86 [-2.26, -1.46]**
Heterogeneity: Tau² = 0.65; Chi² = 173.57, df = 18 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 9.08 (P < 0.00001)								



Test for subgroup differences: Chi² = 7.24, df = 1 (P = 0.007), I² = 86.2%

FIGURE 2 | Forest plot of heart dose (D_{mean} and Dmax) between the DIBH group and FB group.

Study or Subgroup	DIBH Mean	DIBH SD	DIBH Total	FB Mean	FB SD	FB Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.2.1 Heart V30								
Chi. F. 2015	1.6	1	31	3.4	1.8	31	7.3%	-1.22 [-1.77, -0.68]
Comsa 2014	0.2	0.3	30	4	3	30	6.8%	-1.76 [-2.36, -1.16]
Dincoglan 2013	2.8	2.4	27	9.2	4.75	27	6.6%	-1.68 [-2.30, -1.05]
Hammadi 2018	2.8	2.3	54	7.8	4	54	8.2%	-1.52 [-1.95, -1.09]
Kunheri 2017	0.55	0.93	45	2.12	1.74	45	8.1%	-1.12 [-1.56, -0.67]
Lawler 2017	0.05	0.18	28	0.47	1.03	28	7.4%	-0.56 [-1.09, -0.03]
Lee 2013	2.8	2.65	25	6.31	3.398	25	6.8%	-1.13 [-1.73, -0.53]
Lin 2019	2.5	3	63	11.4	5.5	121	8.8%	-1.85 [-2.21, -1.49]
Pham 2016 (IMRT Group)	5.3	4.5	15	14.5	6.2	15	5.1%	-1.65 [-2.50, -0.81]
Pham 2016 (VMAT Group)	1	1.1	15	3.7	3.2	15	5.5%	-1.10 [-1.87, -0.32]
Saini 2018	0	0.126	33	1.15	1.563	33	7.5%	-1.02 [-1.54, -0.51]
Saini 2019(supine position)	0	0.119	25	0.91	1.222	25	6.9%	-1.03 [-1.62, -0.44]
Tanguturi 2015	0	2.95	110	1.5	4.625	38	8.7%	-0.43 [-0.80, -0.06]
Wiant 2015	0	0	25	2.2	3.8	25		Not estimable
Zhao-Feng 2018 (3D-CRT Group)	0.36	0.57	22	2.62	2.26	22	6.3%	-1.35 [-2.01, -0.69]
Zhao-Feng 2018 (IMRT Group)	0	0	22	0.07	0.09	22		Not estimable
Subtotal (95% CI)			**570**			**556**	**100.0%**	**-1.23 [-1.49, -0.97]**
Heterogeneity: Tau² = 0.17; Chi² = 44.26, df = 13 (P < 0.0001); I² = 71%								
Test for overall effect: Z = 9.17 (P < 0.00001)								
1.2.3 Heart V10								
Chi. F. 2015	4.4	2.2	31	6.3	2.2	31	6.5%	-0.85 [-1.37, -0.33]
Comsa 2014	1.6	2	30	8	4	30	5.8%	-2.00 [-2.62, -1.37]
Dincoglan 2013	6	3.25	27	13.3	6.25	27	5.9%	-1.44 [-2.05, -0.84]
Hammadi 2018	4.9	3.2	54	11.2	5	54	7.2%	-1.49 [-1.92, -1.06]
Hepp 2015	1	0.4	20	6.5	3.4	20	4.7%	-2.23 [-3.03, -1.42]
Kunheri 2017	2.72	2.18	45	8.19	4.54	45	6.9%	-1.52 [-1.99, -1.05]
Lastrucci 2017	1.2	2.5	23	4.1	3.7	23	5.9%	-0.90 [-1.51, -0.29]
Lin 2019	6	4.7	63	18.6	7.3	121	7.6%	-1.92 [-2.28, -1.56]
Pham 2016 (IMRT Group)	10	6.5	15	21.5	8.5	15	4.6%	-1.48 [-2.30, -0.66]
Pham 2016 (VMAT Group)	10.6	6	15	20.2	8.9	15	4.8%	-1.23 [-2.02, -0.44]
Saini 2018	0.11	0.637	33	2.66	2.33	33	6.3%	-1.48 [-2.02, -0.93]
Saini 2019(prone position)	0.003	0.067	25	0.02	0.193	25	6.3%	-0.12 [-0.67, 0.44]
Saini 2019(supine position)	0.001	0.548	25	2.46	1.993	25	5.6%	-1.66 [-2.31, -1.01]
Schönecker 2016	0.26	0.39	9	4.12	3.45	9	3.4%	-1.50 [-2.57, -0.42]
Yamauchi 2020	0.3	0.8	85	1.9	2.2	85	7.9%	-0.96 [-1.28, -0.64]
Zhao-Feng 2018 (3D-CRT Group)	0.93	1.17	22	4.57	3.07	22	5.4%	-1.54 [-2.22, -0.86]
Zhao-Feng 2018 (IMRT Group)	0.68	0.84	22	4.01	2.32	22	5.2%	-1.87 [-2.59, -1.15]
Subtotal (95% CI)			**544**			**602**	**100.0%**	**-1.40 [-1.65, -1.15]**
Heterogeneity: Tau² = 0.18; Chi² = 53.03, df = 16 (P < 0.00001); I² = 70%								
Test for overall effect: Z = 10.90 (P < 0.00001)								
1.2.4 Heart V5								
Angela 2017	1.8	1.3	32	5.4	3.5	32	6.8%	-1.35 [-1.89, -0.80]
Dincoglan 2013	8.4	4.5	27	17	6.8	27	6.6%	-1.47 [-2.08, -0.86]
Eldredge 2015	3	9.3	86	11.1	14.95	86	7.2%	-0.65 [-0.95, -0.34]
Kunheri 2017	4.74	2.94	45	11.68	5.43	45	6.9%	-1.58 [-2.05, -1.10]
Lastrucci 2017	2.1	3.5	23	7.5	7	23	6.6%	-0.96 [-1.57, -0.35]
Liuwei 2021	0.23	0.18	11	2.68	1.19	11	4.9%	-2.77 [-4.00, -1.54]
Pham 2016 (IMRT Group)	16.1	9.2	15	29.4	10.8	15	6.1%	-1.29 [-2.09, -0.49]
Pham 2016 (VMAT Group)	5.7	1.4	15	8.1	2	15	6.1%	-1.35 [-2.16, -0.55]
Rochet 2015	1.5	0.2	35	8.2	0.7	35	2.7%	-12.87 [-15.12, -10.63]
Saini 2018	0.9	1.259	33	4.81	3.422	33	6.8%	-1.50 [-2.05, -0.95]
Saini 2019(prone position)	0.15	0.319	25	0.24	0.563	25	6.7%	-0.19 [-0.75, 0.36]
Saini 2019(supine position)	0.3	1.844	25	4.53	2.748	25	6.5%	-1.78 [-2.44, -1.12]
Schönecker 2016	1.18	0.77	9	6.75	4.39	9	5.2%	-1.68 [-2.80, -0.57]
Tanguturi 2015	3.8	10.3	110	8	11.05	38	7.1%	-0.40 [-0.77, -0.03]
Yamauchi 2020	0.7	1.2	85	3.1	2.7	85	7.2%	-1.14 [-1.47, -0.82]
Zhao-Feng 2018 (3D-CRT Group)	2.57	2.05	22	7.78	4.2	22	6.4%	-1.55 [-2.23, -0.87]
Subtotal (95% CI)			**598**			**526**	**100.0%**	**-1.58 [-2.05, -1.12]**
Heterogeneity: Tau² = 0.75; Chi² = 160.71, df = 15 (P < 0.00001); I² = 91%								
Test for overall effect: Z = 6.68 (P < 0.00001)								



Test for subgroup differences: Chi² = 1.91, df = 2 (P = 0.38), I² = 0%

FIGURE 3 | Forest plot of heart dose (V30, V10 and V5) between the DIBH group and FB group.

Study or Subgroup	DIBH Mean	DIBH SD	DIBH Total	FB Mean	FB SD	FB Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.3.1 LAD Dmean (cGy)								
Angela 2017	555.7	355.1	32	1,568.6	1,049.1	32	2.1%	-1.28 [-1.82, -0.74]
Bruzzaniti 2013(CF)	274	168.8	8	901	665	8	1.4%	-1.22 [-2.32, -0.13]
Bruzzaniti 2013(HF)	186	114.8	8	612	452	8	1.4%	-1.22 [-2.32, -0.13]
Christina 2021	620	430	97	1,050	870	97	2.3%	-0.62 [-0.91, -0.34]
Dincoglan 2013	971.4	493.5	27	3,669	1,227	27	1.8%	-2.84 [-3.61, -2.07]
Dolezel 2021	467	280	100	2,471	1,130	100	2.3%	-2.43 [-2.79, -2.06]
Ferini 2021	555	549	116	1,527	1,018	116	2.4%	-1.18 [-1.46, -0.91]
Goyal 2020 (prone position)	262.31	254.61	14	261.59	270.59	14	1.8%	0.00 [-0.74, 0.74]
Hammadi 2018	1,480	760	54	2,300	670	54	2.2%	-1.14 [-1.54, -0.73]
Jensen 2017	1,300	1,140	22	2,810	1,330	22	1.9%	-1.20 [-1.84, -0.55]
Jiheon 2020	580	430	75	1,460	660	75	2.3%	-1.57 [-1.94, -1.20]
Kunheri 2017	606.56	369.19	45	1,320.64	444.84	45	2.1%	-1.73 [-2.22, -1.24]
Lastrucci 2017	660	840	23	1,800	1,200	23	2.0%	-1.08 [-1.70, -0.46]
Lawler 2017	522.6	194.3	28	1,088.4	395.3	28	2.0%	-1.79 [-2.42, -1.16]
Lee 2013	1,601	734.5	25	2,626	1,129	25	2.0%	-1.06 [-1.65, -0.46]
Liuwei 2021	221	33	11	304	75	11	1.5%	-1.38 [-2.33, -0.43]
Misra 2021	445	414	30	1,099	918	30	2.1%	-0.91 [-1.44, -0.37]
Mohamad 2017	939.7	580.5	22	2,125	982.6	22	1.9%	-1.44 [-2.11, -0.77]
Pham 2016 (IMRT Group)	2,600	950	15	3,900	680	15	1.7%	-1.53 [-2.36, -0.70]
Pham 2016 (VMAT Group)	1,740	580	15	2,470	650	15	1.7%	-1.15 [-1.93, -0.37]
Rochet 2015	400	420	35	1,490	940	35	2.1%	-1.48 [-2.01, -0.95]
Saini 2018	630	429.6	33	2,173	1,478	33	2.1%	-1.40 [-1.94, -0.86]
Saini 2019(prone position)	349	208.9	25	496	230.4	25	2.0%	-0.66 [-1.23, -0.09]
Saini 2019(supine position)	388	399.3	25	2,238	1,544	25	1.9%	-1.61 [-2.26, -0.97]
Sakka 2017 (IMRT Group)	580	68	20	640	88	20	1.9%	-0.75 [-1.39, -0.10]
Sakka 2017 (VMAT Group)	731	97	20	872	176	20	1.9%	-0.97 [-1.63, -0.31]
Sakyanun 2020	1,148	810	25	1,984	1,020	25	2.0%	-0.89 [-1.48, -0.31]
Schönecker 2016	419	152	9	1,891	978	9	1.3%	-2.00 [-3.19, -0.82]
Vikström 2011	640	760	17	1,810	1,250	17	1.8%	-1.10 [-1.83, -0.38]
Wang 2012	594.6	437.4	53	2,047.4	493	53	2.0%	-3.09 [-3.67, -2.52]
Zhao-Feng 2018 (3D-CRT Group)	1,022	1,030	22	2,908	1,672	22	1.9%	-1.33 [-1.99, -0.67]
Zhao-Feng 2018 (IMRT Group)	735	542	22	1,610	745	22	1.9%	-1.32 [-1.98, -0.66]
Subtotal (95% CI)			**1073**			**1073**	**61.5%**	**-1.35 [-1.57, -1.13]**
Heterogeneity: Tau² = 0.30; Chi² = 148.69, df = 31 (P < 0.00001); I² = 79%								
Test for overall effect: Z = 12.03 (P < 0.00001)								
1.3.2 LAD Dmax (cGy)								
Angela 2017	2,364.8	1,475.6	32	3,895.9	1,230.2	32	2.1%	-1.11 [-1.64, -0.58]
Bruzzaniti 2013(CF)	425	225	8	1,962	1,225	8	1.3%	-1.65 [-2.83, -0.47]
Bruzzaniti 2013(HF)	310	175	8	1,675	1,100	8	1.3%	-1.64 [-2.82, -0.46]
Christina 2021	1,540	1,030	97	2,350	1,390	97	2.3%	-0.66 [-0.95, -0.37]
Dincoglan 2013	1,974.8	1,182	27	4,679.4	972	27	1.8%	-2.46 [-3.18, -1.74]
Dolezel 2021	993	1,100	100	4,904	1,130	100	2.2%	-3.49 [-3.94, -3.05]
Ferini 2021	1,771	1,425	116	3,599	1,292	116	2.3%	-1.34 [-1.62, -1.05]
Goyal 2020 (prone position)	838.96	1,108.48	14	991.54	1,166.83	14	1.8%	-0.13 [-0.87, 0.61]
Hammadi 2018	4,430	1,220	54	4,970	340	54	2.2%	-0.60 [-0.98, -0.21]
Jensen 2017	1,300	1,140	22	2,810	1,330	22	1.9%	-1.20 [-1.84, -0.55]
Kunheri 2017	2,196.62	1,085.22	45	3,439.11	423.14	45	2.2%	-1.50 [-1.97, -1.03]
Lawler 2017	1,555.5	1,061.5	28	2,982	1,005.1	28	2.0%	-1.36 [-1.95, -0.78]
Lee 2013	4,165	1,195	25	4,727	913.8	25	2.0%	-0.52 [-1.08, 0.04]
Liuwei 2021	594	215	11	1,229	592	11	1.5%	-1.37 [-2.32, -0.42]
Misra 2021	1,322	1,180	30	2,820	1,130	30	2.0%	-1.28 [-1.84, -0.72]
Pham 2016 (IMRT Group)	4,450	790	15	5,060	160	15	1.8%	-1.04 [-1.81, -0.27]
Pham 2016 (VMAT Group)	3,330	890	15	4,090	600	15	1.8%	-0.97 [-1.74, -0.21]
Rochet 2015	1,860	1,750	35	4,190	1,720	35	2.1%	-1.33 [-1.85, -0.81]
Sakka 2017 (IMRT Group)	1,228	349	20	1,493	394	20	1.9%	-0.70 [-1.34, -0.06]
Sakka 2017 (VMAT Group)	1,545	560	20	2,115	630	20	1.9%	-0.94 [-1.59, -0.28]
Subtotal (95% CI)			**722**			**722**	**38.5%**	**-1.26 [-1.61, -0.90]**
Heterogeneity: Tau² = 0.54; Chi² = 158.75, df = 19 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 6.97 (P < 0.00001)								
Total (95% CI)			**1795**			**1795**	**100.0%**	**-1.32 [-1.50, -1.13]**
Heterogeneity: Tau² = 0.38; Chi² = 309.15, df = 51 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 13.57 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.66), I² = 0%								

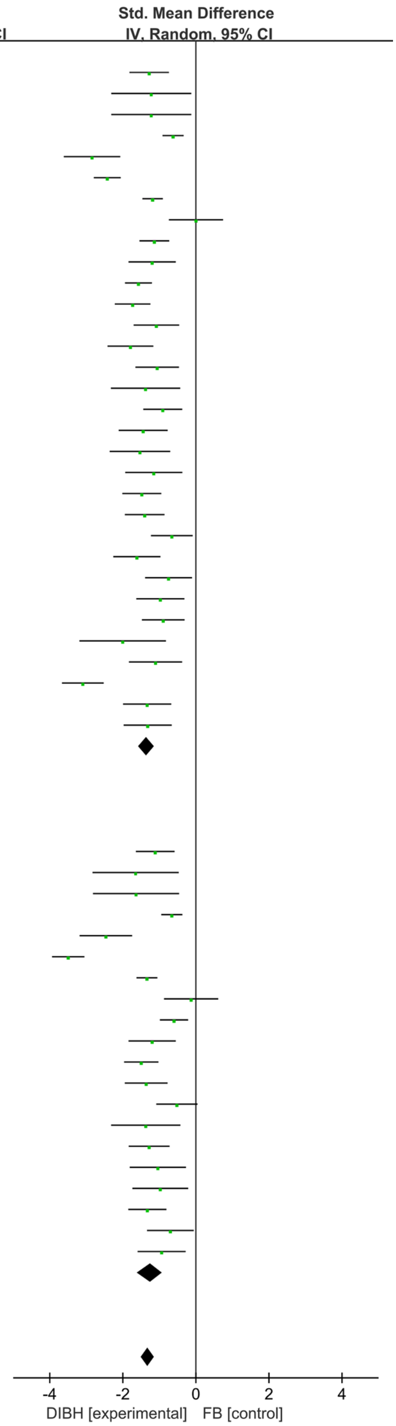


FIGURE 4 | Forest plot of LAD dose (D_{mean} and Dmax) between the DIBH group and FB group.

Publication Bias

A funnel plot was applied for the assessment of publication bias in the literature, tests for the funnel plot asymmetry were applied if there were at least 10 studies included in the meta-analysis. From the funnel plot of different indicators (**Figure 10**), it is evident that the point estimates are symmetrically distributed on both sides, centralized in the middle, therefore showing no evidence of publication bias.

Study or Subgroup	DIBH Mean	DIBH SD	DIBH Total	FB Mean	FB SD	FB Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.4.1 Ipsilateral Lung Dmean (cGy)								
Bruzzaniti 2013(CF)	464	72.25	8	551	132.5	8	1.8%	-0.77 [-1.80, 0.26]
Bruzzaniti 2013(HF)	315	47.75	8	375	90.25	8	1.8%	-0.79 [-1.81, 0.24]
Chi. F. 2015	645.2	156.5	31	795.2	129.3	31	3.2%	-1.03 [-1.56, -0.50]
Comsa 2014	1,116	199	30	1,426	283	30	3.1%	-1.25 [-1.81, -0.69]
Dincoglan 2013	1,505.3	302	27	1,877	379	27	3.1%	-1.07 [-1.64, -0.50]
Dolezel 2021	832	188	100	999	242	100	4.0%	-0.77 [-1.06, -0.48]
Eldredge 2015	590	299	86	640	431.8	86	4.0%	-0.13 [-0.43, 0.17]
Ferini 2021	643	201	116	744	276	116	4.1%	-0.42 [-0.68, -0.16]
Goyal 2020 (prone position)	87.46	44.81	14	65.23	52.78	14	2.5%	0.44 [-0.31, 1.19]
Hammadi 2018	1,060	260	54	1,130	320	54	3.7%	-0.24 [-0.62, 0.14]
Hepp 2015	630	80	20	870	10	20	1.6%	-4.13 [-5.26, -2.99]
Jiheon 2020	520	120	75	580	170	75	3.9%	-0.41 [-0.73, -0.08]
Kunheri 2017	608.75	159.36	45	646.08	234.78	45	3.6%	-0.18 [-0.60, 0.23]
Lastrucci 2017	466	160	23	610	130	23	2.9%	-0.97 [-1.58, -0.36]
Lawler 2017	716	237.9	28	815	374.3	28	3.2%	-0.31 [-0.84, 0.22]
Lee 2013	753	134	25	804	169.8	25	3.1%	-0.33 [-0.89, 0.23]
Lin 2019	895.2	139.6	63	1,173.1	263.8	121	3.9%	-1.21 [-1.54, -0.88]
Liuwei 2021	477	86	11	629	135	11	2.0%	-1.29 [-2.23, -0.36]
Mohamad 2017	1,498	282.3	22	1,803	279	22	2.8%	-1.07 [-1.70, -0.43]
Pham 2016 (IMRT Group)	1,830	250	15	2,180	290	15	2.4%	-1.26 [-2.05, -0.46]
Pham 2016 (VMAT Group)	1,820	90	15	1,820	110	15	2.6%	0.00 [-0.72, 0.72]
Rochet 2015	700	230	35	770	450	35	3.4%	-0.19 [-0.66, 0.28]
Saini 2018	554	157.8	33	563	194.8	33	3.4%	-0.05 [-0.53, 0.43]
Saini 2019(prone position)	88	51.11	25	69	29.63	25	3.1%	0.45 [-0.11, 1.01]
Saini 2019(supine position)	541	144.4	25	609	220	25	3.1%	-0.36 [-0.92, 0.20]
Sakka 2017 (IMRT Group)	1,042	71	20	1,079	89	20	2.9%	-0.45 [-1.08, 0.18]
Sakka 2017 (VMAT Group)	989	103	20	1,027	106	20	2.9%	-0.36 [-0.98, 0.27]
Schönecker 2016	645	131	9	801	202	9	1.9%	-0.87 [-1.85, 0.11]
Vikström 2011	590	100	17	690	120	17	2.6%	-0.88 [-1.59, -0.18]
Wang 2012	503.6	157.7	53	520.9	150.9	53	3.7%	-0.11 [-0.49, 0.27]
Yamauchi 2020	513.1	195.7	85	566.3	232.2	85	4.0%	-0.25 [-0.55, 0.06]
Zhao-Feng 2018 (3D-CRT Group)	690	160	22	777	271	22	3.0%	-0.38 [-0.98, 0.21]
Zhao-Feng 2018 (IMRT Group)	562	105	22	590	224	22	3.0%	-0.16 [-0.75, 0.43]
Subtotal (95% CI)			**1182**			**1240**	**100.0%**	**-0.55 [-0.73, -0.37]**

Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 132.27$, df = 32 (P < 0.00001); $I^2 = 76\%$

Test for overall effect: Z = 6.05 (P < 0.00001)

Test for subgroup differences: Not applicable

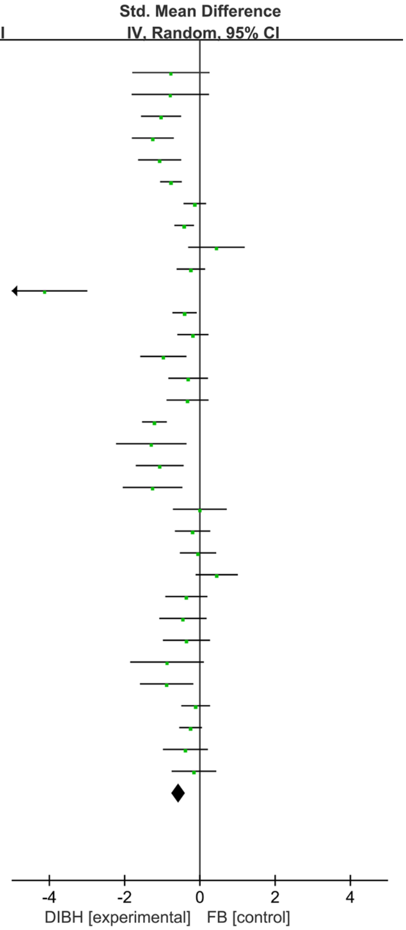


FIGURE 5 | Forest plot of ipsilateral lung dose (D_{mean}) between the DIBH group and FB group.

DISCUSSION

There are many studies on the incidence of RRHD caused by radiotherapy for breast cancer. The research of Darby et al. (3) in 2013 showed that exposure of the heart to ionizing radiation during radiotherapy for breast cancer increases the subsequent rate of ischemic heart disease. The increase is proportional to the mean dose to the heart, beginning within a few years after exposure, and continues for at least 20 years. Women with preexisting cardiac risk factors have greater absolute increases in risk from radiotherapy than other women. Additionally, further studies indicate that LAD coronary artery doses may be particularly relevant to RRHD risks, since this artery is a common site of atherosclerosis inducing myocardial infarction. It is the site of high doses in many left-breast cancer radiotherapy regimens, and may well contribute to radiation-induced heart disease (58). Some recent research has focused on the relationship between the average cardiac dose and the incidence of adverse events. One such research conducted by Van den Bogaard et al. concluded that the cumulative incidence of acute coronary events increased by 16.5% per Gy (59). A study by Dutch et al. showed that the risk of myocardial infarction increased linearly as the mean of the whole heart dose increased, with an excess risk ratio of 6.4% per Gy (60).. In another Ebbe Laugaard Lorenzen et al. study, it was demonstrated that for female patients receiving tangential field irradiation, the linear increase in the excess odds ratio of major coronary events per gray of mean heart dose was 19% (61). Therefore, to reduce the incidence of RRHD, the deposition dose of heart and LAD should be low enough. In this paper, we respectively studied the dosimetric indexes of heart and LAD. The results implied that the dose of the heart and LAD in the DIBH group was significantly lower than that in the FB group. The meta-analysis results of all subgroups of cardiac dose (D_{mean}, D_{max}, V30, V10, and V5) and LAD dose subgroup (D_{mean}, D_{max}) support this conclusion unanimously (**Figures 2–4**). We have reason to believe that DIBH may reduce RRHD more effectively by reducing the dose to the heart and LAD, such as ischemic heart disease, acute coronary event and myocardial infarction. Moreover, the results of this study infer that different radiotherapy techniques (3D-CRT, IMRT or VMAT), postural design (supine or prone position) and prescribed dose schemes

Study or Subgroup	DIBH Mean	DIBH SD	DIBH Total	FB Mean	FB SD	FB Total	Weight	Mean Difference IV, Random, 95% CI
1.5.1 Ipsilateral Lung V20								
Bruzzaniti 2013(CF)	6.11	1.79	8	8.13	2.54	8	2.9%	-2.02 [-4.17, 0.13]
Bruzzaniti 2013(HF)	5.71	1.85	8	7.65	2.45	8	2.9%	-1.94 [-4.07, 0.19]
Chi. F. 2015	9.2	2.6	31	13	3	31	3.3%	-3.80 [-5.20, -2.40]
Christina 2021	22.5	5.9	97	27.3	6.8	97	3.1%	-4.80 [-6.59, -3.01]
Comsa 2014	22	5	30	28	6	30	2.5%	-6.00 [-8.79, -3.21]
Dincoglan 2013	27.2	4.75	27	32.4	6.5	27	2.3%	-5.20 [-8.24, -2.16]
Dolezel 2021	13.59	3.92	100	17.87	5.38	100	3.4%	-4.28 [-5.58, -2.98]
Eldredge 2015	10.4	6.31	86	12	9.3	86	2.7%	-1.60 [-3.98, 0.78]
Ferini 2021	10.71	4.56	116	13.06	6.25	116	3.3%	-2.35 [-3.76, -0.94]
Hammadi 2018	19.5	5.1	54	20.5	7	54	2.8%	-1.00 [-3.31, 1.31]
Hepp 2015	12	1.5	20	17	2.1	20	3.5%	-5.00 [-6.13, -3.87]
Jensen 2017	13.3	1.8	22	13.5	2.5	22	3.4%	-0.20 [-1.49, 1.09]
Jiheon 2020	9.9	3.1	75	11.2	4.4	75	3.4%	-1.30 [-2.52, -0.08]
Kunheri 2017	13.14	4.16	45	14.4	6.03	45	2.9%	-1.26 [-3.40, 0.88]
Lastrucci 2017	8.9	3.1	23	11.7	3	23	3.1%	-2.80 [-4.56, -1.04]
Lee 2013	14.63	2.71	25	15.72	3.385	25	3.2%	-1.09 [-2.79, 0.61]
Lin 2019	17.4	3.1	63	23.2	5.7	63	3.2%	-5.80 [-7.40, -4.20]
Liuwei 2021	8.1	2.51	11	12.13	3.65	11	2.6%	-4.03 [-6.65, -1.41]
Misra 2021	12.31	5.54	30	17.09	7.22	30	2.2%	-4.78 [-8.04, -1.52]
Mohamad 2017	31.93	6.69	22	38.41	7.16	22	1.8%	-6.48 [-10.57, -2.39]
Pham 2016 (IMRT Group)	36.9	5.5	15	44	6.2	15	1.7%	-7.10 [-11.29, -2.91]
Pham 2016 (VMAT Group)	34.4	3.3	15	35.3	3.4	15	2.7%	-0.90 [-3.30, 1.50]
Rochet 2015	13.7	0.9	35	16.4	1.5	35	3.7%	-2.70 [-3.28, -2.12]
Saini 2018	9.34	3.659	33	9.84	4.881	33	2.9%	-0.50 [-2.58, 1.58]
Saini 2019(prone position)	0.49	0.815	25	0.16	0.341	25	3.7%	0.33 [-0.02, 0.68]
Saini 2019(supine position)	9.5	3.385	25	10.94	4.83	25	2.8%	-1.44 [-3.75, 0.87]
Sakyanun 2020	19.72	4.3	25	22.73	6.1	25	2.4%	-3.01 [-5.94, -0.08]
Schönecker 2016	10.96	3.1	9	14.87	4.41	9	2.1%	-3.91 [-7.43, -0.39]
Shim 2012	10.98	4.22	10	13.18	4.17	10	2.0%	-2.20 [-5.88, 1.48]
Stranzl 2009	15.29	3.52	11	17.78	1.96	11	2.7%	-2.49 [-4.87, -0.11]
Vikström 2011	10	1.9	17	12.2	2.4	17	3.3%	-2.20 [-3.66, -0.74]
Wang 2012	9.6	4.375	53	10.4	3.775	53	3.2%	-0.80 [-2.36, 0.76]
Yamauchi 2020	9.2	4.4	85	10.4	5.2	85	3.3%	-1.20 [-2.65, 0.25]
Zhao-Feng 2018 (3D-CRT Group)	11.26	3.68	22	13.37	5.77	22	2.4%	-2.11 [-4.97, 0.75]
Zhao-Feng 2018 (IMRT Group)	9.83	3.01	22	11.12	5.55	22	2.6%	-1.29 [-3.93, 1.35]
Subtotal (95% CI)			**1295**			**1295**	**100.0%**	**-2.62 [-3.37, -1.87]**
Heterogeneity: Tau² = 3.84; Chi² = 279.67, df = 34 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 6.88 (P < 0.00001)								
1.5.2 Ipsilateral Lung V10								
Bruzzaniti 2013(CF)	9.08	2.48	8	11.54	3.25	8	5.7%	-2.46 [-5.29, 0.37]
Bruzzaniti 2013(HF)	8.32	2.32	8	10.7	3.03	8	6.1%	-2.38 [-5.02, 0.26]
Chi. F. 2015	13	3	31	16.5	3	31	8.6%	-3.50 [-4.99, -2.01]
Comsa 2014	29	5	30	35	6	30	5.8%	-6.00 [-8.79, -3.21]
Eldredge 2015	13.7	7.64	86	15	11.29	86	5.6%	-1.30 [-4.18, 1.58]
Hammadi 2018	25.4	5.8	54	25.9	8.1	54	6.1%	-0.50 [-3.16, 2.16]
Hepp 2015	16	1.5	20	21.5	2.3	20	9.2%	-5.50 [-6.70, -4.30]
Jiheon 2020	14.4	3.7	75	16.4	5.3	75	8.7%	-2.00 [-3.46, -0.54]
Kunheri 2017	17.48	4.87	45	18.6	6.78	45	6.5%	-1.12 [-3.56, 1.32]
Lin 2019	24.5	3.9	63	29	6.3	121	8.6%	-4.50 [-5.98, -3.02]
Liuwei 2021	11.07	2.86	11	15.81	4.05	11	5.6%	-4.74 [-7.67, -1.81]
Saini 2018	13.14	4.837	33	13.27	5.481	33	6.4%	-0.13 [-2.62, 2.36]
Saini 2019(supine position)	13.24	3.689	25	14.7	5.874	28	6.2%	-1.46 [-4.07, 1.15]
Zhao-Feng 2018 (3D-CRT Group)	15.96	4.05	22	17.63	6.23	22	5.2%	-1.67 [-4.78, 1.44]
Zhao-Feng 2018 (IMRT Group)	14.49	3.21	22	15.95	6.21	22	5.6%	-1.46 [-4.38, 1.46]
Subtotal (95% CI)			**533**			**594**	**100.0%**	**-2.71 [-3.71, -1.72]**
Heterogeneity: Tau² = 2.43; Chi² = 43.54, df = 14 (P < 0.0001); I² = 68%								
Test for overall effect: Z = 5.33 (P < 0.00001)								
1.5.3 Ipsilateral Lung V5								
Comsa 2014	40	5	30	45	6	30	5.8%	-5.00 [-7.79, -2.21]
Eldredge 2015	20.9	19.6	86	22.9	21.9	86	2.2%	-2.00 [-8.21, 4.21]
Hepp 2015	23	1.7	20	27	2.4	20	8.7%	-4.00 [-5.29, -2.71]
Jiheon 2020	21.1	4.6	75	23.8	6.4	75	7.7%	-2.70 [-4.48, -0.92]
Kunheri 2017	22.1	5.6	45	22.91	7.19	45	6.0%	-0.81 [-3.47, 1.85]
Lastrucci 2017	17.7	4.9	23	20.5	4	23	6.2%	-2.80 [-5.39, -0.21]
Lin 2019	33.2	5	63	36	7.1	121	7.7%	-2.80 [-4.57, -1.03]
Liuwei 2021	18.82	2.82	11	23.23	4.03	11	5.6%	-4.41 [-7.32, -1.50]
Pham 2016 (IMRT Group)	56.1	4.9	15	61.8	5.9	15	4.1%	-5.70 [-9.58, -1.82]
Pham 2016 (VMAT Group)	90	5.5	15	89.3	5.8	15	3.9%	0.70 [-3.35, 4.75]
Rochet 2015	26.7	1.2	35	29.4	1.8	35	9.6%	-2.70 [-3.42, -1.98]
Saini 2019(prone position)	2.03	2.363	25	1.26	1.022	25	9.2%	0.77 [-0.24, 1.78]
Saini 2019(supine position)	21.12	4.904	25	21.9	3.622	25	6.5%	-0.78 [-3.17, 1.61]
Yamauchi 2020	17.7	5.9	85	18.1	6.5	85	7.5%	-0.40 [-2.27, 1.47]
Zhao-Feng 2018 (3D-CRT Group)	24.94	4.8	22	25.53	7.35	22	4.4%	-0.59 [-4.26, 3.08]
Zhao-Feng 2018 (IMRT Group)	22.82	3.79	22	22.84	7.01	22	4.9%	-0.02 [-3.35, 3.31]
Subtotal (95% CI)			**597**			**655**	**100.0%**	**-2.08 [-3.11, -1.04]**
Heterogeneity: Tau² = 2.76; Chi² = 62.38, df = 15 (P < 0.00001); I² = 76%								
Test for overall effect: Z = 3.95 (P < 0.0001)								

Test for subgroup differences: Chi² = 0.93, df = 2 (P = 0.63), I² = 0%

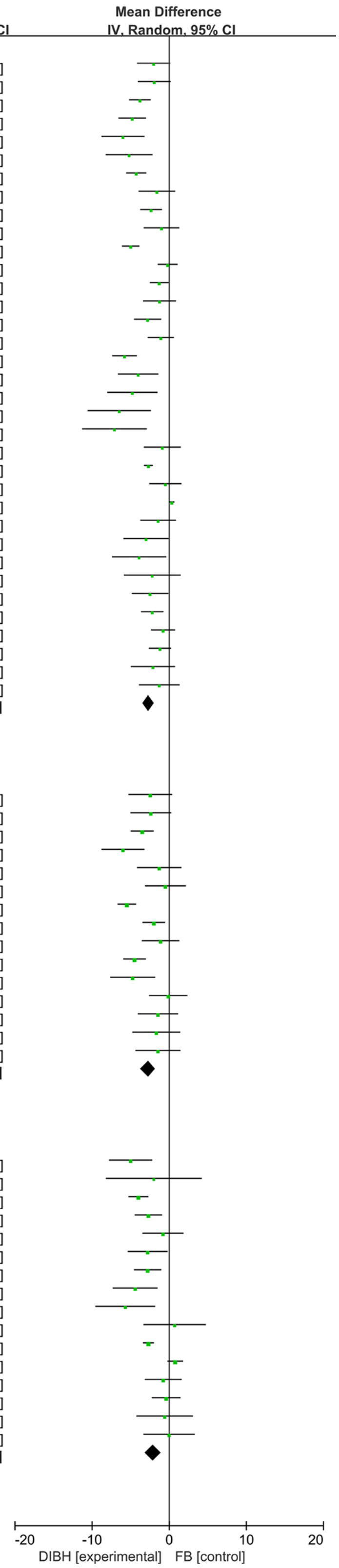


FIGURE 6 | Forest plot of ipsilateral lung dose (V20, V10 and V5) between the DIBH group and FB group.

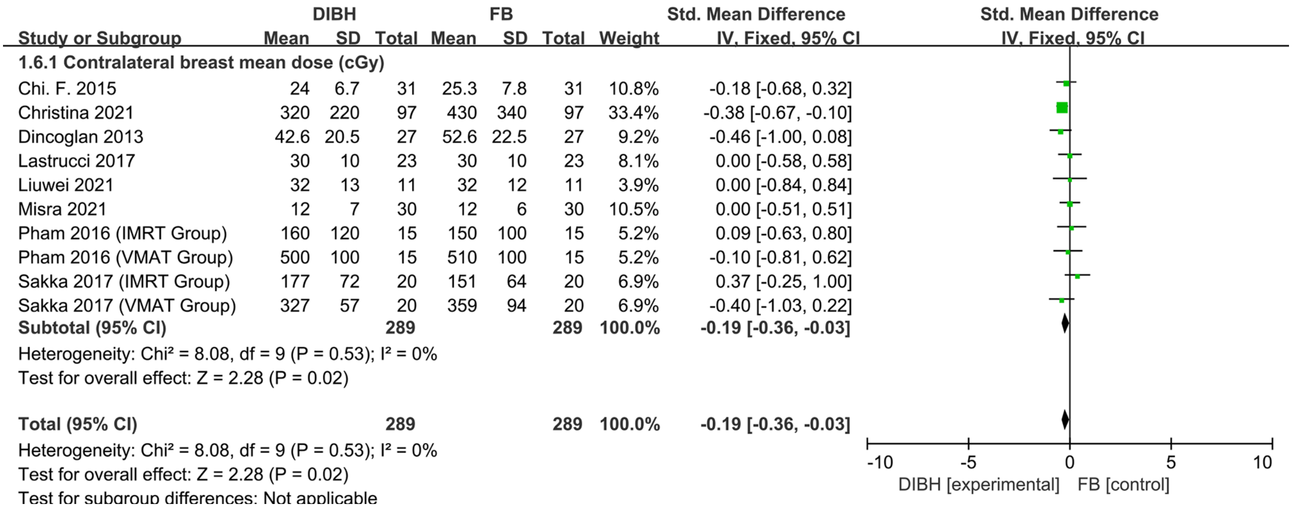


FIGURE 7 | Forest plot of contralateral breast mean dose between the DIBH group and FB group.

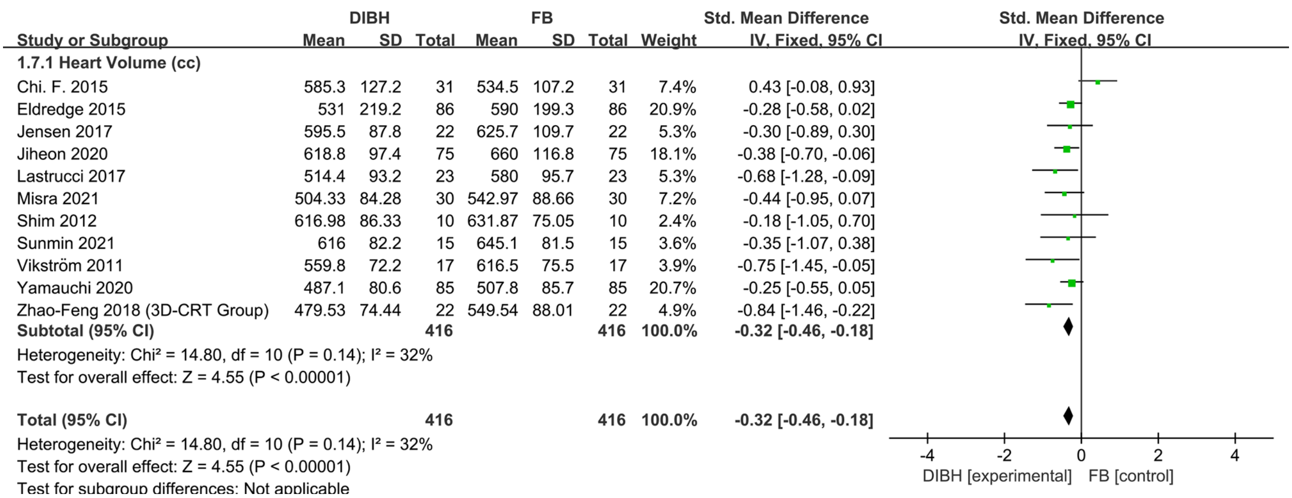


FIGURE 8 | Forest plot of heart volume between the DIBH group and FB group.

(CF or HF) did not affect the dose reduction advantages of DIBH compared with FB in the heart and LAD.

In 1998, Kwa et al. (62) conducted a large multicenter study of 530 people on the relationship between the incidence of radiation pneumonitis and dose distribution in the lungs. Their results showed that increasing pneumonitis rate was observed with increasing mean lung dose in all centers. Especially in the low dose range of 4 to 16 Gy, the incidence rate of pneumonia in the breast group was 1.4%. Therefore, the mean lung dose can be used as a useful predictor of the risk of radiation pneumonia. Additionally, research conducted by Gokula et al. and Kasmann et al. implied that Locoregional radiotherapy increased the mean lung dose, and ipsilateral lung volume receiving 20 Gy (V20) >30% have been identified as risk factors for RP (63, 64). In this study, ipsilateral lung dosimetric indicators (D_{mean}, V20, V10, and V5) were extracted from 33 studies totaling 2768 patients. Compared to the FB group, left-sided breast cancer patients could benefit more from DIBH technology. The subgroup analysis results are presented in **Figures 5** and **6**, D_{mean} (SMD = -0.55, 95%, CI: -0.73 ~ -0.37, P<0.01), V20 (SMD = -2.62, 95% CI: -3.37 ~ -1.87 P < 0.01), V10 (SMD = -2.71, 95% CI: -3.71 ~ -1.72, P <0.01), V5 (SMD = -2.08, 95% CI: -3.11 ~ -1.04, P<0.01). We can conclude that DIBH technology may reduce the incidence of RP by reducing the mean lung dose, V20, V10, and V5. However, there are a few exceptions. It can be seen from the forest plot (**Figures 5** and **6**) that DIBH did not perform better than FB in all prone position groups. Therefore, large sample size experiments are needed to focus on the difference

Study or Subgroup	DIBH Mean	DIBH SD	DIBH Total	FB Mean	FB SD	FB Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.8.1 Ipsilateral lung volume (cc)								
Chi. F. 2015	1,757.1	354.5	31	1,023.2	197.8	31	3.6%	2.52 [1.85, 3.20]
Dolezel 2021	2,150	400.6	100	1,228	308.1	100	11.8%	2.57 [2.19, 2.95]
Eldredge 2015	1,969	461.7	86	1,145	345.5	86	12.3%	2.01 [1.64, 2.38]
Ferini 2021	2,219.1	462.7	116	1,286.8	337	116	15.0%	2.30 [1.96, 2.63]
Hammadi 2018	1,557	389	54	914	207.7	54	7.6%	2.05 [1.58, 2.52]
Jensen 2017	2,098.2	250.2	22	1,283.1	298.8	22	2.2%	2.90 [2.04, 3.77]
Jiheon 2020	2,213.2	442.8	75	1,272.8	372.5	75	9.7%	2.29 [1.87, 2.70]
Lastrucci 2017	2,086.3	422	23	1,302.3	255.4	23	3.0%	2.21 [1.46, 2.96]
Misra 2021	1,445	308.6	30	811	164	30	3.5%	2.53 [1.84, 3.22]
Nissen 2013	2,156	400	144	1,247	249	83	12.8%	2.57 [2.21, 2.93]
Shim 2012	1,459.51	302.71	10	1,005.52	180.48	10	1.5%	1.74 [0.68, 2.81]
Sunmin 2021	1,600.7	409.4	15	923.1	227.6	15	2.1%	1.99 [1.09, 2.89]
Vikström 2011	2,165.1	509.9	17	1,178.2	343.2	17	2.2%	2.22 [1.34, 3.09]
Yamauchi 2020	2,132	337.6	85	1,395.9	241.6	85	10.2%	2.50 [2.09, 2.90]
Zhao-Feng 2018 (3D-CRT Group)	1,663.36	270.93	22	1,022.22	223.48	22	2.5%	2.54 [1.72, 3.35]
Subtotal (95% CI)			**830**			**769**	**100.0%**	**2.35 [2.22, 2.48]**
Heterogeneity: Chi² = 12.66, df = 14 (P = 0.55); I² = 0%								
Test for overall effect: Z = 35.65 (P < 0.00001)								
Total (95% CI)			**830**			**769**	**100.0%**	**2.35 [2.22, 2.48]**
Heterogeneity: Chi² = 12.66, df = 14 (P = 0.55); I² = 0%								
Test for overall effect: Z = 35.65 (P < 0.00001)								
Test for subgroup differences: Not applicable								

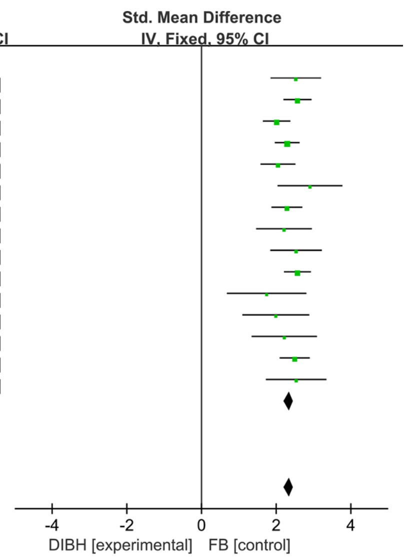


FIGURE 9 | Forest plot of ipsilateral lung volume between the DIBH group and FB group.

between DIBH technology and FB in dissimilar postures. In addition, the results of this study infer that different radiotherapy techniques (3D-CRT, IMRT or VMAT) and prescribed dose schemes (CF or HF) did not affect the dose reduction advantages of DIBH compared with FB in the ipsilateral lung.

Further, we counted and analyzed the mean dose of contralateral breast, heart volume, and ipsilateral lung volume. The combined analysis showed between the two groups there was no significant difference in contralateral breast mean dose and there was no statistical significance (SMD = - 0.19, 95% CI: - 0.36 ~ -0.03, P=0.02). Meanwhile, results indicated that the ipsilateral lung volume increased significantly in the DIBH group (SMD = 2.35, 95% CI: 2.22 ~ 2.48, P<0.01), while the heart volume was compressed (SMD = -0.32, 95% CI: -0.46 ~ -0.18, P<0.01). This phenomenon is not difficult to understand, because DIBH is a simple technique used to reduce cardiac exposure by lung expansion which physically displaces the heart out of the radiation field. Objectively speaking, the use of DIBH technology expands the lung volume, which in turn makes the contralateral breast farther away from the radiation field, and finally the contralateral breast should have a lower mean dose. However, in the FB group, the contralateral breast was also almost outside the field, which made the DIBH group have no significant advantage in reducing the mean breast dose compared with the FB group.

Potential limitations exist in this study, and the meta-analysis without the distinction of surgical operation is an obvious one. In left-sided breast cancer patients with modified radical mastectomy (MRM), the target (i.e., chest wall) lies near the heart and LAD, as compared to those patients undergoing breast conservation surgery (BCS). Recently, a small sample study by Misra et al. showed that DIBH provided a similar percentage reduction in cardiopulmonary doses for both MRM and BCS. Significant reductions in mean heart dose were seen in both groups. Although lung and LAD doses were significantly reduced in MRM, lung dosimetric constraints were less frequently achieved in the subgroup with nodal radiation. Given that, we appeal to researchers to conduct more studies about the relationship between surgical methods and the benefits of DIBH technology, enabling more left-sided breast cancer patients to benefit from the development of precision medicine.

Apart from the distinction of surgical operation mode, other potential limitations are still prevalent in this study: (1) The data from the included studies were from the published articles instead of the original information of the individual patient; (2) all included articles are the retrospective studies, and the evidence level is lower than that of prospective randomized clinical trials; (3) the number of included studies is relatively small, especially for contralateral breast mean dose, which may cause bias results; (4) the heterogeneity of aggregated results were significant, and the random-effects model was applied to most indicators.

CONCLUSIONS

In summary, this study provides a large-scale and comprehensive meta-analysis between the dosimetric parameters of DIBH and FB for left-sided breast cancer. Although DIBH has no obvious advantage over FB in contralateral breast mean dose, it can significantly reduce the heart dose, LAD dose, ipsilateral lung dose, heart volume, and substantially increase the ipsilateral lung volume. This study suggests that DIBH may be more widely used in clinical practice soon because of its excellent dosimetric performance.

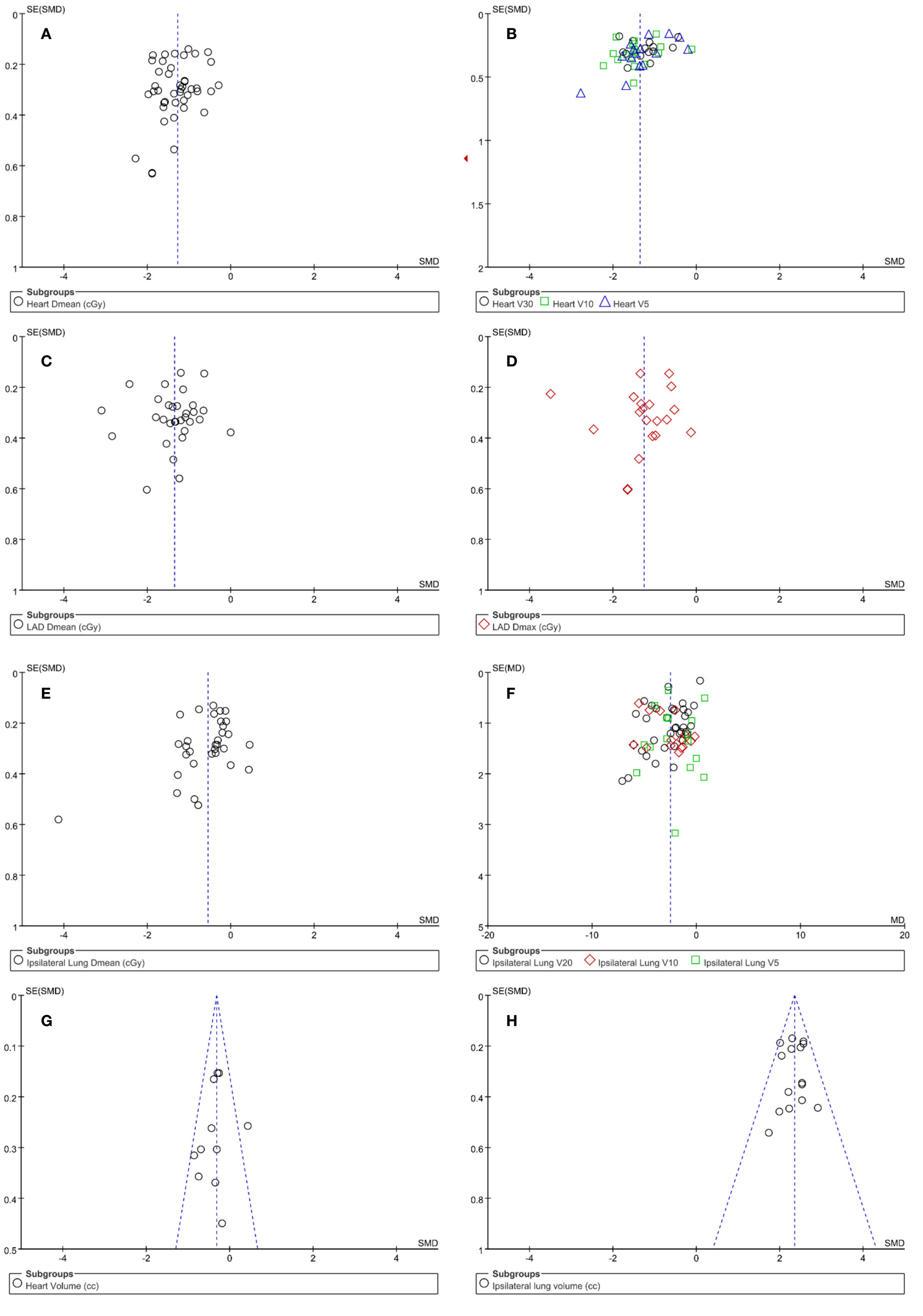


FIGURE 10 | Funnel plots for potential publication bias. Funnel plot analysis of heart dose **(A, B)**, LAD dose **(C, D)**, ipsilateral lung dose **(E, F)**, heart volume **(G)** and ipsilateral lung volume **(H)**.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

YKL, DY, and XZ: conceptualization. YL, WY, YZ, FT: data curation and original draft writing. YKL, YT, RH: statistical analysis. YL, JP, BH, RC: manuscript review and editing. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin* (2021) 71(1):7–33. doi: 10.3322/caac.21654
2. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al. Effects of Radiotherapy and of Differences in the Extent of Surgery for Early Breast Cancer on Local Recurrence and 15-Year Survival: An Overview of the Randomised Trials. *Lancet* (2005) 366(9503):2087–106. doi: 10.1016/s0140-6736(05)67887-7
3. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, et al. Risk of Ischemic Heart Disease in Women After Radiotherapy for Breast Cancer. *N Engl J Med* (2013) 368(11):987–98. doi: 10.1056/NEJMoa1209825
4. Cox JD, Stetz J, Pajak TF. Toxicity Criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* (1995) 31 (5):1341–6. doi: 10.1016/0360-3016(95)00060-c
5. Yamauchi R, Mizuno N, Itazawa T, Saitoh H, Kawamori J. Dosimetric Evaluation of Deep Inspiration Breath Hold for Left-Sided Breast Cancer: Analysis of Patient-Specific Parameters Related to Heart Dose Reduction. *J Radiat Res* (2020) 61(3):447–56. doi: 10.1093/jrr/rraa006
6. Rutqvist LE, Lax I, Fornander T, Johansson H. Cardiovascular Mortality In A Randomized Trial Of Adjuvant Radiation-Therapy Versus Surgery Alone In Primary Breast-Cancer. *Int J Radiat Oncol Biol Phys* (1992) 22(5):887–96. doi: 10.1016/0360-3016(92)90784-f
7. Saini AS, Das IJ, Hwang CS, Biagioli MC, Lee WE 3rd. Biological Indices Evaluation of Various Treatment Techniques for Left-Sided Breast Treatment. *Pract Radiat Oncol* (2019) 9(6):e579–90. doi: 10.1016/j.prro.2019.06.020
8. Grantzau T, Thomsen MS, Væth M, Overgaard J. Risk of Second Primary Lung Cancer in Women After Radiotherapy for Breast Cancer. *Radiother Oncol* (2014) 111(3):366–73. doi: 10.1016/j.radonc.2014.05.004
9. Hayden AJ, Rains M, Tiver K. Deep Inspiration Breath Hold Technique Reduces Heart Dose From Radiotherapy for Left-Sided Breast Cancer. *J Med Imaging Radiat Oncol* (2012) 56(4):464–72. doi: 10.1111/j.1754-9485.2012.02405.x
10. Shah C, Badiyan S, Berry S, Khan AJ, Goyal S, Schulte K, et al. Cardiac Dose Sparing and Avoidance Techniques in Breast Cancer Radiotherapy. *Radiother Oncol* (2014) 112(1):9–16. doi: 10.1016/j.radonc.2014.04.009
11. Yeung R, Conroy L, Long K, Walrath D, Li H, Smith W, et al. Cardiac Dose Reduction With Deep Inspiration Breath Hold for Left-Sided Breast Cancer Radiotherapy Patients With and Without Regional Nodal Irradiation. *Radiat Oncol* (2015) 10(1):200. doi: 10.1186/s13014-015-0511-8
12. McIntosh A, Shoushtari AN, Benedict SH, Read PW, Wijesooriya K. Quantifying the Reproducibility of Heart Position During Treatment and Corresponding Delivered Heart Dose in Voluntary Deep Inhalation Breath Hold for Left Breast Cancer Patients Treated With External Beam Radiotherapy. *Int J Radiat OncolBiolPhys* (2011) 81(4):e569–76. doi: 10.1016/j.ijrobp.2011.01.044
13. Wang W, Purdie TG, Rahman M, Marshall A, Liu F-F, Fyles A. Rapid Automated Treatment Planning Process to Select Breast Cancer Patients for Active Breathing Control to Achieve Cardiac Dose Reduction. *Int J Radiat OncolBiolPhys* (2012) 82(1):386–93. doi: 10.1016/j.ijrobp.2010.09.026
14. Bartlett FR, Colgan RM, Carr K, Donovan EM, McNair HA, Locke I, et al. The UK HeartSpare Study: Randomised Evaluation of Voluntary Deep-Inspiratory Breath-Hold in Women Undergoing Breast Radiotherapy. *Radiother Oncol* (2013) 108(2):242–7. doi: 10.1016/j.radonc.2013.04.021
15. Shuster J. Review: Cochrane Handbook for Systematic Reviews for Interventions, Version 5.1.0, Published 3/2011. Julian P.T. Higgins and Sally Green, Editors. *Res Synthesis Methods* (2011) 2(2):126–30. doi: 10.1002/jrsm.38
16. Stang A. Critical Evaluation of the Newcastle-Ottawa Scale for the Assessment of the Quality of Nonrandomized Studies in Meta-Analyses. *Eur J Epidemiol* (2010) 25(9):603–5. doi: 10.1007/s10654-010-9491-z
17. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. Cochrane Handbook for Systematic Reviews of Interventions Version 6.1 (Updated September 2020). In: *Cochrane* (2020). Available at: www.training.cochrane.org/handbook.
18. DerSimonian R, Laird N. Meta-Analysis in Clinical Trials. *Controlled Clin Trials* (1986) 7(3):177–88. doi: 10.1016/0197-2456(86)90046-2
19. Mantel N, Haenszel W. Statistical Aspects of the Analysis of Data From Retrospective Studies of Disease. *J Natl Cancer Inst* (1959) 22(4):719–48. doi: 10.1016/0021-9681(79)90031-6
20. Lin A, Sharieff W, Juhasz J, Whelan T, Kim DH. The Benefit of Deep Inspiration Breath Hold: Evaluating Cardiac Radiation Exposure in Patients After Mastectomy and After Breast-Conserving Surgery. *Breast Cancer (Tokyo Japan)* (2017) 24(1):86–91. doi: 10.1007/s12282-016-0676-5
21. Bruzzaniti V, Abate A, Pinnarò P, D'Andrea M, Infusino E, Landoni V, et al. Dosimetric and Clinical Advantages of Deep Inspiration Breath-Hold (DIBH) During Radiotherapy of Breast Cancer. *J Exp Clin Cancer Res: CR* (2013) 32 (1):88. doi: 10.1186/1756-9966-32-88
22. Chatterjee S, Chakraborty S, Moses A, Nallathambi C, Mahata A, Mandal S, et al. Resource Requirements and Reduction in Cardiac Mortality From Deep Inspiration Breath Hold (DIBH) Radiation Therapy for Left Sided Breast Cancer Patients: A Prospective Service Development Analysis. *Pract Radiat Oncol* (2018) 8(6):382–7. doi: 10.1016/j.prro.2018.03.007
23. Chi F, Wu S, Zhou J, Li F, Sun J, Lin Q, et al. Dosimetric Comparison of Moderate Deep Inspiration Breath-Hold and Free-Breathing Intensity-Modulated Radiotherapy for Left-Sided Breast Cancer. *Cancer Radiotherapie: J la Societe Francaise Radiotherapie Oncologique* (2015) 19 (3):180–6. doi: 10.1016/j.canrad.2015.01.003
24. Schröder C, Kirschke S, Blank E, Rohrberg S, Förster R, Buchali A. Deep Inspiration Breath-Hold for Patients With Left-Sided Breast Cancer – A One-Fits-All Approach? A Prospective Analysis of Patient Selection Using Dosimetrical and Practical Aspects. *Br J Radiol* (2021) 94:20210295. doi: 10.1259/bjr.20210295
25. Comsa D, Barnett E, Le K, Mohamoud G, Zaremski D, Fenkell L, et al. Introduction of Moderate Deep Inspiration Breath Hold for Radiation Therapy of Left Breast: Initial Experience of a Regional Cancer Center. *Pract Radiat Oncol* (2014) 4(5):298–305. doi: 10.1016/j.prro.2013.10.006
26. Dincoglan F, Beyzadeoglu M, Sager O, Oysul K, Kahya YE, Gamsiz H, et al. Dosimetric Evaluation of Critical Organs at Risk in Mastectomized Left-Sided Breast Cancer Radiotherapy Using Breath-Hold Technique. *Tumori* (2013) 99 (1):76–82. doi: 10.1700/1248.13792
27. Dolezel M, Odrazka K, Vanasek J. Deep-Inspiration Breath Hold Radiotherapy in Patients With Left-Sided Breast Cancer After Partial

Mastectomy. *Rozhledy v Chirurgii: Mesicnik Ceskoslovenske Chirurgicke Spolecnosti* (2021) 100(4):180–5. doi: 10.33699/pis.2021.100.4

28. Eldredge-Hindy H, Lockamy V, Crawford A, Nettleton V, Werner-Wasik M, Siglin J, et al. Active Breathing Coordinator Reduces Radiation Dose to the Heart and Preserves Local Control in Patients With Left Breast Cancer: Report of a Prospective Trial. *Pract Radiat Oncol* (2015) 5(1):4–10. doi: 10.1016/j.prro.2014.06.004
29. Ferini G, Molino L, Tripoli A, Valenti V, Illari SI, Marchese VA, et al. Anatomical Predictors of Dosimetric Advantages for Deep-Inspiration-Breath-Hold 3D-Conformal Radiotherapy Among Women With Left Breast Cancer. *Anticancer Res* (2021) 41(3):1529–38. doi: 10.21873/anticanres.14912
30. Goyal U, Saboda K, Roe D, Gonzalez VJ. Prone Positioning With Deep Inspiration Breath Hold for Left Breast Radiotherapy. *Clin Breast Cancer* (2020) 21(4):e295–301. doi: 10.1016/j.clbc.2020.11.004
31. Al-Hammadi N, Caparrotti P, Naim C, Hayes J, Rebecca Benson K, Vasic A, et al. Voluntary Deep Inspiration Breath-Hold Reduces the Heart Dose Without Compromising the Target Volume Coverage During Radiotherapy for Left-Sided Breast Cancer. *Radiol Oncol* (2018) 52(1):112–20. doi: 10.1515/raon-2018-0008
32. Hepp R, Ammerpohl M, Morgenstern C, Nielinger L, Erichsen P, Abdallah A, et al. Deep Inspiration Breath-Hold (DIBH) Radiotherapy in Left-Sided Breast Cancer: Dosimetrical Comparison and Clinical Feasibility in 20 Patients. *Strahlentherapie und Onkologie: Organ der Deutschen Rontgengesellschaft [et al]* (2015) 191(9):710–6. doi: 10.1007/s00066-015-0838-y
33. Jensen CA, Abramova T, Frengen J, Lund J. Monitoring Deep Inspiration Breath Hold for Left-Sided Localized Breast Cancer Radiotherapy With an in-House Developed Laser Distance Meter System. *J Appl Clin Med Phys* (2017) 18(5):117–23. doi: 10.1002/acm2.12137
34. Song J, Tang T, Caudrelier JM, Bélec J, Chan J, Lacasse P, et al. Dose-Sparing Effect of Deep Inspiration Breath Hold Technique on Coronary Artery and Left Ventricle Segments in Treatment of Breast Cancer. *Radiother Oncol: J Eur Soc Ther Radiol Oncol* (2020) 154:101–9. doi: 10.1016/j.radonc.2020.09.019
35. Kunheri B, Kotne S, Nair SS, Makuny D. A Dosimetric Analysis of Cardiac Dose With or Without Active Breath Coordinator Moderate Deep Inspiratory Breath Hold in Left Sided Breast Cancer Radiotherapy. *J Cancer Res Ther* (2017) 13(1):56–61. doi: 10.4103/jcrt.JCRT_1414_16
36. Lastrucci L, Borghesi S, Bertocci S, Gasperi C, Rampini A, Buonfrate G, et al. Advantage of Deep Inspiration Breath Hold in Left-Sided Breast Cancer Patients Treated With 3D Conformal Radiotherapy. *Tumori* (2017) 103 (1):72–5. doi: 10.5301/tj.5000563
37. Lawler G, Leech M. Dose Sparing Potential of Deep Inspiration Breath-Hold Technique for Left Breast Cancer Radiotherapy Organs-At-Risk. *Anticancer Res* (2017) 37(2):883–90. doi: 10.21873/anticanres.11394
38. Lee HY, Chang JS, Lee IJ, Park K, Kim YB, Suh CO, et al. The Deep Inspiration Breath Hold Technique Using Abches Reduces Cardiac Dose in Patients Undergoing Left-Sided Breast Irradiation. *Radiat Oncol J* (2013) 31(4):239–46. doi: 10.3857/roj.2013.31.4.239
39. Lin CH, Lin LC, Que J, Ho CH. A Seven-Year Experience of Using Moderate Deep Inspiration Breath-Hold for Patients With Early-Stage Breast Cancer and Dosimetric Comparison. *Medicine* (2019) 98(19):e15510. doi: 10.1097/md.0000000000015510
40. Tang L, Ishikawa Y, Ito K, Yamamoto T, Umezawa R, Jingu K. Evaluation of DIBH and VMAT in Hypofractionated Radiotherapy for Left-Sided Breast Cancers After Breast-Conserving Surgery: A Planning Study. *Technol Cancer Res Treat* (2021) 20:15330338211048706. doi: 10.1177/15330338211048706
41. Misra S, Mishra A, Lal P, Srivastava R, Verma M, Senthil Kumar SK, et al. Cardiac Dose Reduction Using Deep Inspiratory Breath Hold (DIBH) in Radiation Treatment of Left Sided Breast Cancer Patients With Breast Conservation Surgery and Modified Radical Mastectomy. *J Med Imaging Radiat Sci* (2021) 52(1):57–67. doi: 10.1016/j.jmir.2020.12.004
42. Mohamad O, Shiao J, Zhao B, Roach K, Ramirez E, Vo DT, et al. Deep Inspiration Breathhold for Left-Sided Breast Cancer Patients With Unfavorable Cardiac Anatomy Requiring Internal Mammary Nodal Irradiation. *Pract Radiat Oncol* (2017) 7(6):e361–7. doi: 10.1016/j.prro.2017.04.006
43. Nissen HD, Appelt AL. Improved Heart, Lung and Target Dose With Deep Inspiration Breath Hold in a Large Clinical Series of Breast Cancer Patients. *Radiother Oncol: J Eur Soc Ther Radiol Oncol* (2013) 106(1):28–32. doi: 10.1016/j.radonc.2012.10.016
44. Pham TT, Ward R, Latty D, Owen C, Gebski V, Chojnowski J, et al. Left-Sided Breast Cancer Loco-Regional Radiotherapy With Deep Inspiration Breath-Hold: Does Volumetric-Modulated Arc Radiotherapy Reduce Heart Dose Further Compared With Tangential Intensity-Modulated Radiotherapy? *J Med Imaging Radiat Oncol* (2016) 60(4):545–53. doi: 10.1111/1754-9485.12459
45. Rochet N, Drake JI, Harrington K, Wolfgang JA, Napolitano B, Sadek BT, et al. Deep Inspiration Breath-Hold Technique in Left-Sided Breast Cancer Radiation Therapy: Evaluating Cardiac Contact Distance as a Predictor of Cardiac Exposure for Patient Selection. *Pract Radiat Oncol* (2015) 5(3):e127–e34. doi: 10.1016/j.prro.2014.08.003
46. Saini AS, Hwang CS, Biagioli MC, Das IJ. Evaluation of Sparing Organs at Risk (OARs) in Left-Breast Irradiation in the Supine and Prone Positions and With Deep Inspiration Breath-Hold. *J Appl Clin Med Phys* (2018) 19(4):195–204. doi: 10.1002/acm2.12382
47. Sakka M, Kunzelmann L, Metzger M, Grabenbauer GG. Cardiac Dose-Sparing Effects of Deep-Inspiration Breath-Hold in Left Breast Irradiation: Is IMRT More Beneficial Than VMAT? *Strahlentherapie und Onkologie: Organ der Deutschen Rontgengesellschaft [et al]* (2017) 193(10):800–11. doi: 10.1007/s00066-017-1167-0
48. Sakyanun P, Saksornchai K, Nantavithya C, Chakkabat C, Shotelersuk K. The Effect of Deep Inspiration Breath-Hold Technique on Left Anterior Descending Coronary Artery and Heart Dose in Left Breast Irradiation. *Radiat Oncol J* (2020) 38(3):181–8. doi: 10.3857/roj.2020.00094
49. Schönecker S, Walter F, Freislederer P, Marisch C, Scheithauer H, Harbeck N, et al. Treatment Planning and Evaluation of Gated Radiotherapy in Left-Sided Breast Cancer Patients Using the Catalyst(TM)/Sentinel(TM) System for Deep Inspiration Breath-Hold (DIBH). *Radiat Oncol (London England)* (2016) 11(1):143. doi: 10.1186/s13014-016-0716-5
50. Shim JG, Kim JK, Park W, Seo JM, Hong CS, Song KW, et al. Dose-Volume Analysis of Lung and Heart According to Respiration in Breast Cancer Patients Treated With Breast Conserving Surgery. *J Breast Cancer* (2012) 15 (1):105–10. doi: 10.4048/jbc.2012.15.1.105
51. Simonetto C, Eidemüller M, Gaasch A, Pazos M, Schönecker S, Reitz D, et al. Does Deep Inspiration Breath-Hold Prolong Life? Individual Risk Estimates of Ischaemic Heart Disease After Breast Cancer Radiotherapy. *Radiother Oncol: J Eur Soc Ther Radiol Oncol* (2019) 131:202–7. doi: 10.1016/j.radonc.2018.07.024
52. Stranzl H, Zurl B, Langsenlehner T, Kapp KS. Wide Tangential Fields Including the Internal Mammary Lymph Nodes in Patients With Left-Sided Breast Cancer. Influence of Respiratory-Controlled Radiotherapy (4D-CT) on Cardiac Exposure. *Strahlentherapie und Onkologie: Organ der Deutschen Rontgengesellschaft [et al]* (2009) 185(3):155–60. doi: 10.1007/s00066-009-1939-2
53. Park S, Rim CH, Yoon WS. Variation of Heart and Lung Radiation Doses According to Setup Uncertainty in Left Breast Cancer. *Radiat Oncol* (2021) 16 (1):78. doi: 10.1186/s13014-021-01806-5
54. Tanguturi SK, Lyatskaya Y, Chen Y, Catalano PJ, Chen MH, Yeo WP, et al. Prospective Assessment of Deep Inspiration Breath-Hold Using 3-Dimensional Surface Tracking for Irradiation of Left-Sided Breast Cancer. *Pract Radiat Oncol* (2015) 5(6):358–65. doi: 10.1016/j.prro.2015.06.002
55. Vikström J, Hjelstuen MH, Mjaaland I, Dybvik KI. Cardiac and Pulmonary Dose Reduction for Tangentially Irradiated Breast Cancer, Utilizing Deep Inspiration Breath-Hold With Audio-Visual Guidance, Without Compromising Target Coverage. *Acta Oncol (Stockholm Sweden)* (2011) 50 (1):42–50. doi: 10.3109/0284186x.2010.512923
56. Wiant D, Wentworth S, Liu H, Sintay B. How Important Is a Reproducible Breath Hold for Deep Inspiration Breath Hold Breast Radiation Therapy? *Int J Radiat Oncol Biol Phys* (2015) 93(4):901–7. doi: 10.1016/j.ijrobp.2015.06.010
57. Zhao F, Shen J, Lu Z, Luo Y, Yao G, Bu L, et al. Abdominal DIBH Reduces the Cardiac Dose Even Further: A Prospective Analysis. *Radiat Oncol (London England)* (2018) 13(1):116. doi: 10.1186/s13014-018-1062-6
58. Taylor CW, Nisbet A, McGale P, Goldman U, Darby SC, Hall P, et al. Cardiac Doses From Swedish Breast Cancer Radiotherapy Since the 1950s. *Radiother Oncol: J Eur Soc Ther Radiol Oncol* (2009) 90(1):127–35. doi: 10.1016/j.radonc.2008.09.029
59. van den Bogaard VAB, Ta BDP, van der Schaaf A, Bouma AB, Middag AMH, Bantema-Joppe EJ, et al. Validation and Modification of a Prediction Model

for Acute Cardiac Events in Patients With Breast Cancer Treated With Radiotherapy Based on Three-Dimensional Dose Distributions to Cardiac Substructures. *J Clin Oncol* (2017) 35(11):1171–8. doi: 10.1200/JCO.2016.69.8480
60. Jacobse JN, Duane FK, Boekel NB, Schaapveld M, Hauptmann M, Hooning MJ, et al. Radiation Dose-Response for Risk of Myocardial Infarction in Breast Cancer Survivors. *Int J Radiat Oncol Biol Phys* (2019) 103(3):595–604. doi: 10.1016/j.ijrobp.2018.10.025
61. Laugaard Lorenzen E, Christian Rehammar J, Jensen M-B, Ewertz M, Brink C. Radiation-Induced Risk of Ischemic Heart Disease Following Breast Cancer Radiotherapy in Denmark, 1977–2005. *Radiother Oncol* (2020) 152:103–10. doi: 10.1016/j.radonc.2020.08.007
62. Kwa SLS, Lebesque JV, Theuws JCM, Marks LB, Munley MT, Bentel G, et al. Radiation Pneumonitis as a Function of Mean Lung Dose: An Analysis of Pooled Data of 540 Patients. *Int J Radiat Oncol Biol Phys* (1998) 42(1):1–9. doi: 10.1016/S0360-3016(98)00196-5
63. Gokula K, Earnest A, Wong LC. Meta-Analysis of Incidence of Early Lung Toxicity in 3-Dimensional Conformal Irradiation of Breast Carcinomas. *Radiat Oncol* (2013) 81–12. doi: 10.1186/1748-717x-8-268
64. Kasmann L, Dietrich A, Staab-Weijnitz CA, Manapov F, Behr J, Rimner A, et al. Radiation-Induced Lung Toxicity - Cellular and Molecular Mechanisms of Pathogenesis, Management, and Literature Review. *Radiat Oncol* (2020) 15 (1):1–16. doi: 10.1186/s13014-020-01654-9

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