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Prone position versus supine position in postoperative radiotherapy for breast cancer

A meta-analysis

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Abstract

Background: This meta-analysis evaluates the difference of sparing organs at risk (OAR) in different position (Prone position and Supine position) with different breathing patterns (Free breathing, FB/Deep inspiration breath hold, DIBH) for breast cancer patients receiving postoperative radiotherapy and provides a useful reference for clinical practice.

Method: The relevant controlled trials of prone position versus supine position in postoperative radiotherapy for breast cancer were retrieved from the sources of PubMed, Cochrane Library, Embase, Web of Science and ClinicalTrails.gov. The principal outcome of interest was OAR doses (heart dose, left anterior descending coronary artery dose and ipsilateral lung dose) and target coverage. We mainly compared the effects of P-FB (Prone position FB) and S-FB (Supine position FB) and discussed the effects of DIBH combined with different positions on OAR dose in postoperative radiotherapy. We calculated summary standardized mean difference (SMD) and 95% confidence intervals (CI). The meta-analysis was performed using RevMan 5.4 software.

Results: The analysis included 751 patients from 19 observational studies. Compared with the S-FB, the P-FB can have lower heart dose, left anterior descending coronary artery (LADCA) dose, and ipsilateral lung dose (ILL) more effectively, and the difference was statistically significant (heart dose, SMD = − 0.51, 95% CI − 0.66 ~ − 0.36, $P < .00001$. LADCA dose, SMD = − 0.58, 95% CI − 0.85 ~ − 0.31, $P < .0001$. ILL dose, SMD = − 2.84, 95% CI − 3.2 ~ − 2.48, $P < .00001$). And there was no significant difference in target coverage between the S-FB and P-FB groups (SMD = − 0.1, 95% CI − 0.57 ~ 0.36, $P = .66$). Moreover, through descriptive analysis, we found that P-DIBH (Prone position DIBH) has better sparing OAR than P-FB and S-DIBH (Supine position DIBH).

Conclusion: By this meta-analysis, compared with the S-FB we found that implementation of P-FB in postoperative radiotherapy for breast cancer can reduce irradiation of heart dose, LADCA dose and ILL dose, without compromising mean dose of target coverage. Moreover, P-DIBH might become the most promising way for breast cancer patients to undergo radiotherapy.

Abbreviations: CI = confidence intervals, DIBH = Deep inspiration breath hold, D_{max} = max dose, D_{mean} = mean dose, FB = Free breathing, ILL = ipsilateral lung, LADCA = left anterior descending coronary artery, OAR = Organs at risk, P = Prone position, RCTs = randomized controlled trials, S = Supine position, SMD = standardized mean difference, V20 = the percentage of the organ volume receiving at least 20 Gy, V30 = the percentage of the organ volume receiving at least 30 Gy, V40 = the percentage of the organ volume receiving at least 40 Gy, V5 = the percentage of the organ volume receiving at least 5 Gy.

Keywords: breast cancer, deep inspiration breath hold, meta-analysis, prone position, radiotherapy, supine position

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1. Introduction

Breast cancer is the most common malignant tumor in women.[1] Postoperative radiotherapy can effectively reduce the local recurrence rate and improve long-term survival rate for early stage breast cancer.[2] EBCTCG showed that postoperative radiotherapy reduced the risk of local recurrence by 19% in 5 years compared with those who did not receive postoperative radiotherapy and reduced the risk of breast cancer deaths by 5% in 15 years.[3] Hence postoperative radiotherapy has become the standard treatment for early stage breast cancer. However, radiotherapy will increase the risk of non-breast cancer related deaths, thereby offsetting the survival advantage of patients.[4,5]

The irradiation of breast tissue will bring a non-negligible dose to the heart and the ILL, which may lead to an increase in the mortality of heart and lung-related diseases.[3,6–11] Heart disease is one of the important reasons for the high mortality in breast cancer patients who accepted postoperative radiotherapy after surviving more than 15 years,[3] and the stenosis of the LADCA is one of the important causes of ischemic heart disease.[8] The incidence of major coronary events increased by 7.4% after every 1 Gy increase in radiation dose and there was no obvious threshold.[9] In addition to cardiac complications, increased lung doses and exposure volume of lung can cause radiation pneumonitis,[10] and the diagnosis rate of lung cancer as a second tumor increases linearly with the increase of radiation dose.[11]

In order to reduce the dose of OAR, some new radiotherapy techniques have been continuously explored. Intensity modulated radiation therapy (IMRT), volume of rotating intensity modulated radiotherapy (VMRT) and proton radiation therapy can effectively reduce the radiation dose of the OAR.[12–16] In addition to the improvement of radiotherapy equipment, DIBH and prone position as two other radiotherapy techniques show great advantages in the protection of OAR as well. DIBH required the patients inhale deeply and hold breath, while in the meantime performs radiotherapy.[17] Our previous research has showed that DIBH after postoperative radiotherapy for left-side breast cancer can reduce the heart dose, LADCA dose and left lung dose without compromising the target coverage.[18] Treatment position is also crucial in radiotherapy. For example, the prone position during radiotherapy for rectal cancer can significantly reduce the small bowel radiation dose compared to the supine position.[19,20] In recent years, clinical studies on different positions with FB or DIBH for postoperative radiotherapy of breast cancer have been reported. However, most studies are limited by small sample size and lack systematic evaluation. We therefore conducted a meta-analysis to provide evidence-based medical basis for its future clinical application.

2. Materials and methods

2.1. Search strategy

A search of the English literature up till July 15, 2020 was conducted using the following electronic databases: PubMed, Cochrane Library, Embase and Web of Science. Search terms included "Breast cancer OR "Breast tumor"; "Breast Neoplasm*" OR "Breast Cancer*" OR "Breast Carcinoma*" OR "Breast Malignanc*" OR "Breast Tumor*" OR "Breast tumour*" OR "Mammary Cancer*" OR "Mammary Neoplasm *"; "radiotherapy"; "radiotherap*" OR "radiat*" OR "irradiat*"; "prone"; "supine". If possible, subject heading terms such as Medical Subject Headings terms were added in all searches. A search of the ClinicalTrials.gov website was also done to identify randomized controlled trials (RCTs) that had been completed but not yet published. All searches were conducted independently by two reviewers (JL and FZ); differences were checked by the two and resolved by discussion.

2.2. Inclusion and exclusion critera

The inclusion criteria were as follows:

1. All studies that compared supine position radiotherapy versus prone position radiotherapy in patients with breast cancer after breast-conserving surgery without metastasis were eligible.
2. Studies with total number of cases greater than or equal to 10.
3. Studies that report on at least 1 of the outcome indicators mentioned in the succeeding portion.
4. Studies in which patients had comorbidities or additional treatments and with non-human trials were excluded.

In addition, abstracts without full text, letters, expert opinions, reviews, conference abstracts without original data, and single case reports were excluded. This analysis was restricted to articles published in English.

2.3. Evaluation index

To investigate the dose homogeneity of target coverage, the mean dose (D_{mean}) and V95% of planning target volume (PTV) were calculated. Furthermore, we compared the dose distributions for the heart, LADCA, and ILL using standard defined parameters: the mean dose (D_{mean}), the maximum dose (D_{max}), and the percentage of the organ volume receiving at least 5 Gy (V5), 20 Gy (V20), 30 Gy (V30) and 40Gy (V40). Data extraction was independently assessed by two reviewers (JL and FZ). Disagreements were resolved by consulting with a third reviewer (JD).

2.4. Quality evaluation

The quality of the cohort studies was assessed by the Newcastle–Ottawa Scale (NOS), judged on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for case–control or cohort studies, respectively. For randomized controlled trials, we used the domains suggested by the Cochrane Handbook for Systematic Reviews of Interventions, including the following aspects: adequacy of the generation of allocation sequence, allocation concealment, blinding, and the presence of incomplete outcome data, selective outcome, or other sources of bias.

2.5. Risk of bias in individual and across studies

Meta-analyses may suffer from several sources of bias. First of all, not all trials lead to a publication, which induces publication bias, and the language of the original publication might give rise to a selection bias. Due to the complexity of the implementation of our research problem (different positions, different positions with different breathing patterns) in distinct clinical treatment centers, most of the enrolled studies were cohort studies and few were randomized controlled studies.

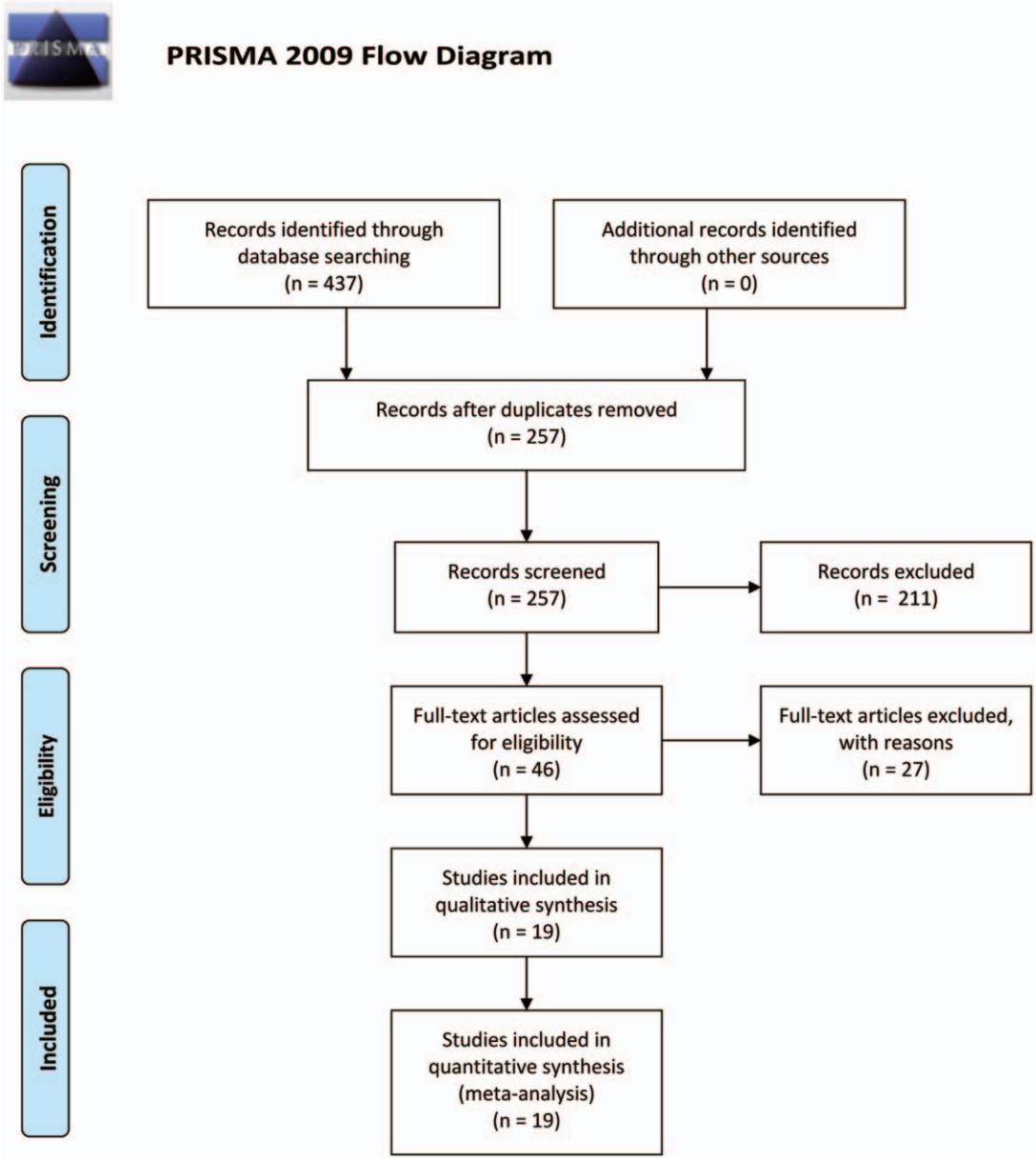

Figure 1. Prisma flow diagram and the process of data selection.

However, reporting bias, confounding and baseline differences might be more pronounced cohort studies, as compared to randomized controlled trials.

2.6. Statistical analysis

Because of the diversity in type of studies, patients, different modern radiotherapy techniques and dose prescription, a random effects model was used. Standardized mean difference (SMD) and 95% CI were used to analyze the effects for measurement data. P value $<.05$ was considered statistically significant. In addition, the funnel plot was used to understand the bias of literature publication. If the points in the funnel plot are symmetrically distributed on both sides around the middlly dashed line and concentrate in the middle, the possibility of publication bias is low. Otherwise, the possibility of publication bias may be high. All statistical analyses were conducted using the Cochrane RevMan 5.4 software.

3. Results

3.1. Included studies

The literature search with our search criteria found 114 articles in PubMed, 5 articles in Cochrane library, 228 articles in Embase, 90 articles in Web of Science and 0 articles in ClinicalTrials.gov. A total of 257 articles remained to be examined after the exclusion of the duplicates. After reading the title and abstract of the article, 46 articles were screened out preliminarily. According to the inclusion criteria and exclusion criteria, 27 articles were screened out again, and 19 articles were finally identified included the final meta-analysis (Fig. 1). Table 1 shows the baseline

Table 1

Baseline characteristics of the included studies.

Studies	Patients numbers L	R	Median age, year P/S	CT scan data (P-FB/S-FB/P-DIBH/S-DIBH)	Stage of cancer	Dose prescription
Buijsen J 2007[21]	7	3	NA	10/10/0/0	ES or CIS	50Gy/25F
Basanta M A 2009[22]	12	8	NA	20/20/0/0	Stage 0-II	50Gy/25F
Varga Z 2009[23]	34	27	56	61/61/0/0	ES	50Gy/25F
Veldeman L 2010[24]	14	4	NA	18/18/0/0	ES or CIS	50Gy/25F
Hannan R 2012[25]	60	69	61.65/66.03	97/32/0/0	Stage 0-II	42.4Gy/16F+9.6Gy/4F
Chen J L-Y 2013[26]	21	0	50.6	21/21/0/0	Stage 0-I	50Gy/25F
Montero F-L A 2013[27]	6	4	50.5	10/10/0/0	Stage 0-II	50Gy/25F
Krengli M 2013[28]	17	24	54.9	41/41/0/0	Tis-2N0-1	50Gy/25F+10Gy/5F
Mulliez T(1) 2013[29]	12	6	NA	18/18/0/0	NA	50Gy/25F
Mulliez T(2) 2013[30]	50	50	58.1/59.6	50/50/0/0	Tis-2N0	40.05Gy/15F
Cammarota F 2014[31]	6	6	53	12/12/0/0	ES	42.56/16F
Fan L-L 2014[32]	10	0	38	10/10/0/0	NA	50Gy/25F
Mulliez T 2015[33]	50	0	55	50/12/50/12	ES	40.05Gy/15F
Kim H 2016[34]	21	0	54	21/21/0/0	Stage0-IA	50.4Gy/28F
Takahashi K 2016[35]	9	13	50	22/22/0/0	Stage 0-II	50Gy/25F
Kahán Z 2018[36]	100	0	NA	100/100/0/0	ES	50Gy/25F
Saini A S 2018[37]	33	0	NA	33/33/0/33	T1-2N0	42.56/16F
Chung Y 2019[38]	50	0	48	50/50/0/0	Tis-2N0-x	50Gy/25F
Saini A S 2019[39]	25	0	NA	25/25/25/25	T1-2N0	42.56/16F

CIS = Carcinoma in situ, DIBH = Deep inspiration breath hold, ES = Early stage, FB = Free breathing, L = left-side breast cancer patients, NA = Not available, P = Prone, R = right-side breast cancer patients, S = Supine.

characteristics of the included studies. The eligible studies include 751 patients (CT scan data of patients in P-FB, S-FB, P-DIBH and S-DIBH group are 669, 566, 75 and 70, respectively). 17 cohort studies were scored using the Newcastle-Ottawa Scale and 2 randomized controlled studies were evaluated using the Cochrane Collaboration's tool for assessing risk of bias.

3.2. Target coverage

We investigated the difference of target coverage between the P-FB group and S-FB group. Our result showed that there was no significant difference in D_{mean} of planning target volume (SMD = − 0.1, 95% CI − 0.57 ~ 0.36, P = .66) (Fig. 2).

3.3. Heart dose

We also investigated the difference in heart dose (D_{mean}, D_{max}, V5, and V30) between the P-FB group and S-FB group. Compared with the S-FB group, the P-FB group can lower heart dose more effectively and the difference was statistically significant (SMD = − 0.51, 95% CI − 0.66 ~ − 0.36, P < .00001). D_{mean} (SMD = − 0.47, 95% CI − 0.75 ~ − 0.19, P = 0.0009), D_{max} (SMD = − 0.57, 95% CI − 0.82 ~ − 0.32, P < .00001), V5 (SMD = − 0.40, 95% CI − 0.63 ~ − 0.16, P = .001), V20 (SMD = − 0.66, 95% CI − 1.05 ~ − 0.26, P = .001) (Fig. 3).

3.4. LADCA dose

Then, we investigated the difference in LADCA dose (D_{mean}, D_{max}, V40) between the P-FB group and S-FB group. Compared with the S-FB group, the P-FB group can reduce LADCA dose more effectively and the difference was statistically significant (SMD = − 0.58, 95% CI − 0.85 ~ − 0.31, P < .0001). D_{mean} (SMD = − 0.53, 95% CI − 0.89 ~ − 0.16, P = .005), D_{max} (SMD = − 0.80, 95% CI − 1.52 ~ − 0.09, P = .03), V40 (SMD = − 0.47, 95% CI − 0.85 ~ − 0.09, P = .01) (Fig. 4).

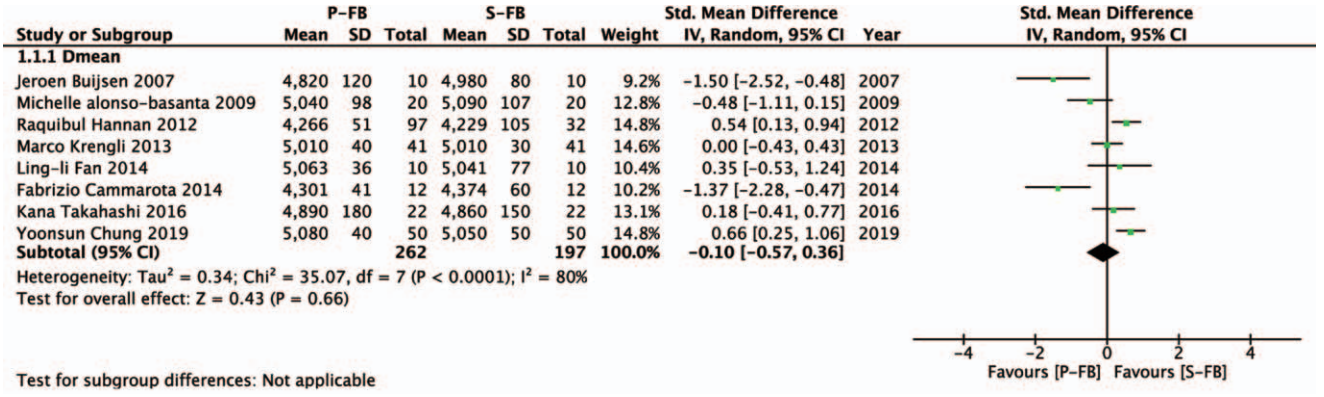

Figure 2. Forest plot of target coverage between the P-FB group and S-FB group.

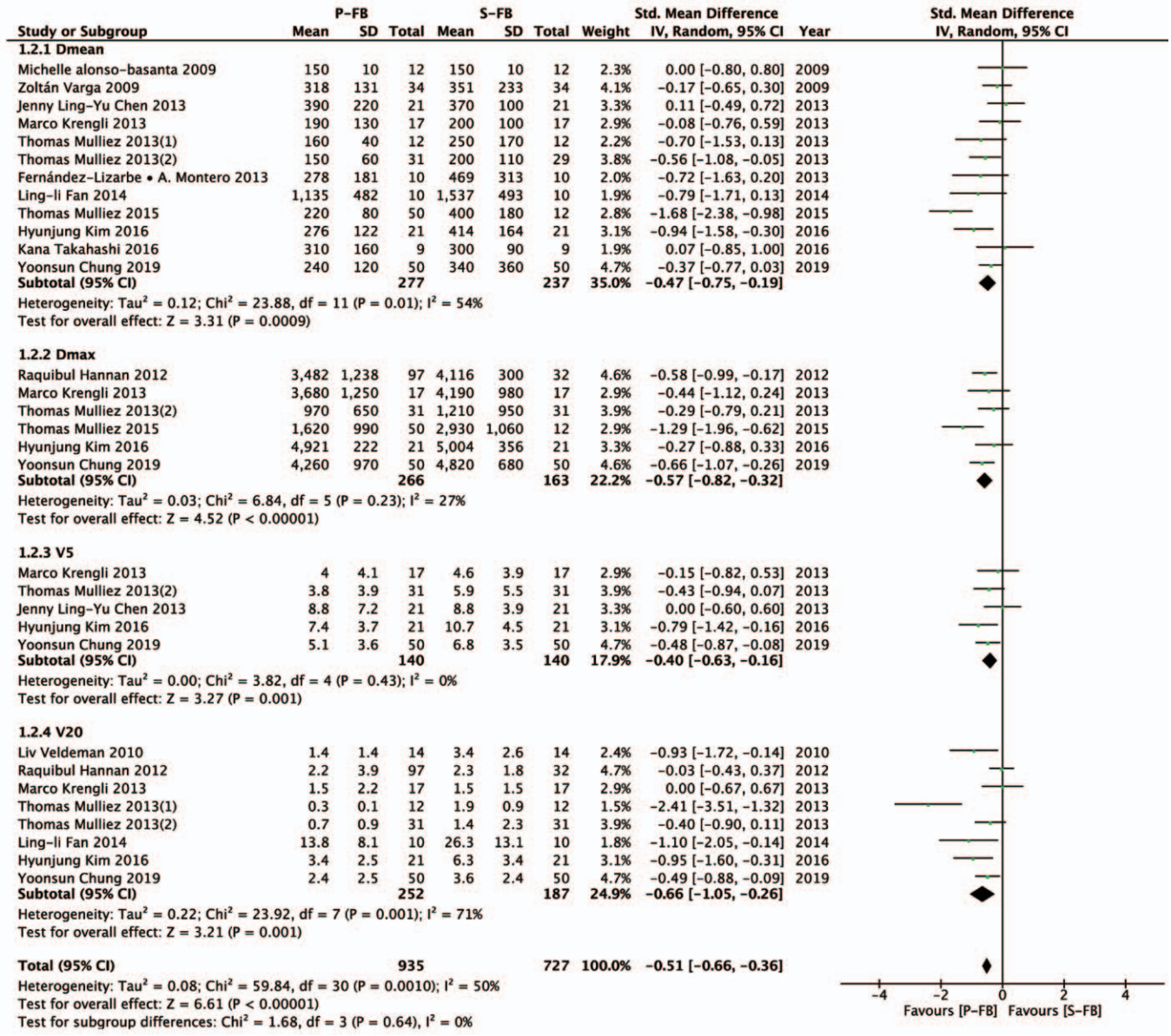

Figure 3. Forest plot of heart dose between the P-FB group and S-FB group.

3.5. ILL dose

Further, we investigated the difference in ILL dose (D_{mean}, D_{max}, V5, and V20) between the P-FB group and S-FB group. Compared with the S-FB group, the P-FB group can also have lower ipsilateral lung dose, and the difference was statistically significant (SMD = − 2.84, 95% CI − 3.2 ~ − 2.48, $P < .00001$). D_{mean} (SMD = − 3.36, 95% CI − 3.95 ~ − 2.77, $P < .00001$), D_{max} (SMD = − 1.89, 95% CI − 2.57 ~ − 1.2, $P < .00001$), V5 (SMD = − 3.21, 95% CI − 4.09 ~ − 2.34, $P < .00001$), V20 (SMD = − 2.54, 95% CI − 3.06 ~ − 2.02, $P < .00001$) (Fig. 5).

3.6. Influence of DIBH with different positions

We further explored the dosimetric effects of DIBH technique with different positions on OAR. Due to the lack of articles containing DIBH with different positions, we conducted only a descriptive analysis for this part data of the included articles rather than quantitative synthesis. Firstly, we analyzed the OAR dose of P-FB vs. S-DIBH (Table 2). Compared to the P-FB, Mulliez et al found that S-DIBH can reduce the dose of heart ($P < .001$), and P-FB reduce the dose of LADCA and ILL ($P < .001$). Saini et al also confirmed that P-FB reduce the dose of ILL ($P < .001$), and there was no significant difference in heart and LADCA between the two groups. Then, we analyzed the OAR dose of P-DIBH vs. S-DIBH (Table 3). Compared to S-DIBH, P-DIBH show dosimetric advantage in OAR (heart, LADCA and ILL) in both studies. Although LADCA dose had no significant statistical difference in Saini's study, the dose of LADCA in P-DIBH is less than S-DIBH.

3.7. Publication bias

From the funnel plot (Fig. 6), it can be seen that the most point estimates are symmetrically distributed on both sides

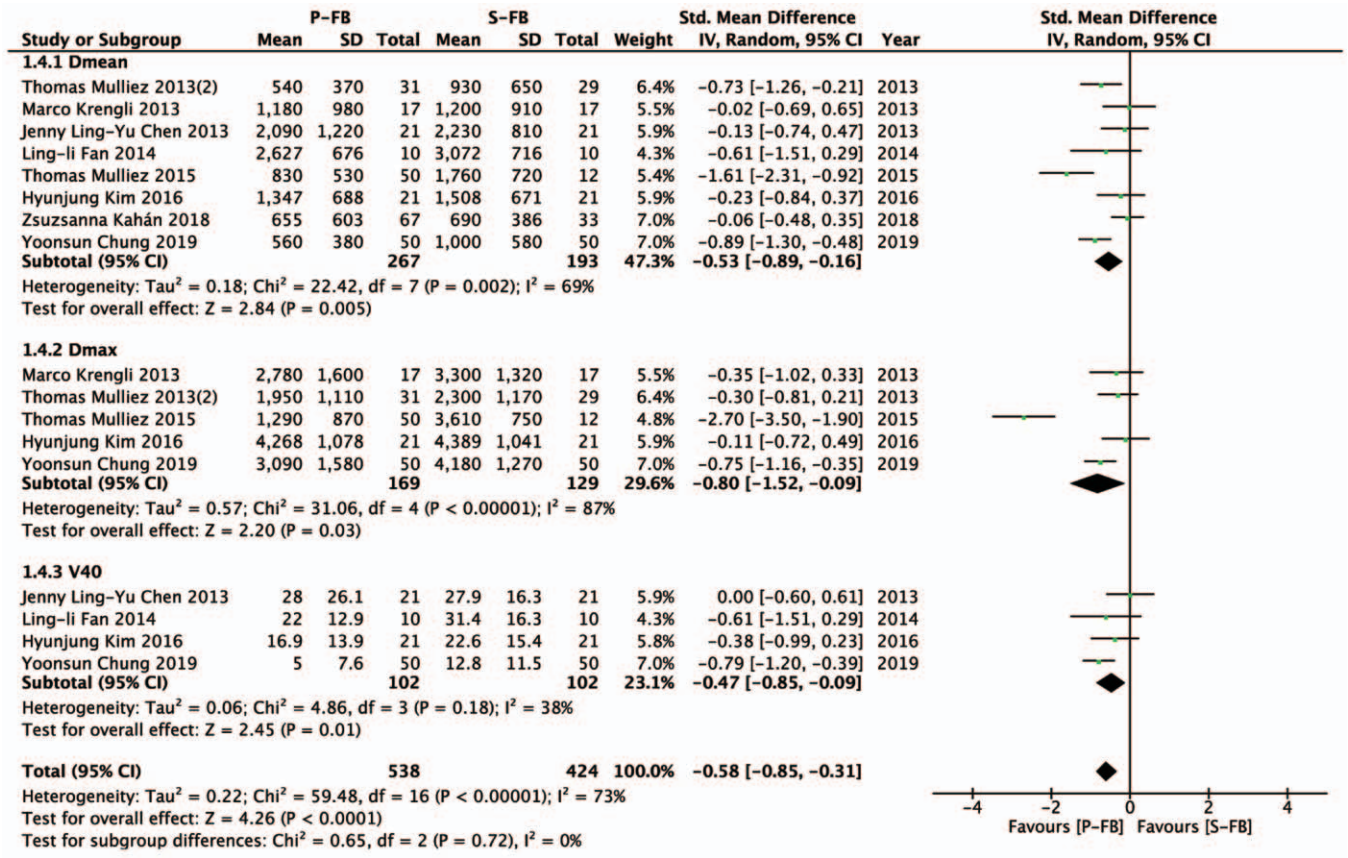

Figure 4. Forest plot of LADCA dose between the P-FB group and S-FB group.

and centralized in the middle, showing no evidence of publication bias.

4. Discussion

How to reduce the dose of OAR in postoperative radiotherapy for breast cancer has been a question that researchers continue to explore. Even if the radiotherapy equipment is updated, radiotherapy is not absolutely safe. Hence, researchers hope to further reduce the dose of OAR by discovering new techniques. Prone positions and DIBH that are two important techniques may have better sparing OAR. In order to explore the sparing OAR of different positions with different breathing patterns in breast cancer patients undergoing postoperative radiotherapy, our study conducted a meta-analysis of OAR doses for P-FB vs. S-FB and do a descriptive analysis that compared OAR doses by using DIBH in different positions.

From our meta-analysis, P-FB group significantly reduced the dose of heart (SMD = − 0.51, 95% CI − 0.66 ~ − 0.36, $P < .00001$), LADCA (MD = − 0.58, 95% CI − 0.85 ~ − 0.31, $P < .0001$) and ILL (SMD = − 2.84, 95% CI − 3.2 ~ − 2.48, $P < .00001$). This result shows that radiotherapy in the prone position can reduce the lower doses than supine position, without compromising D_{mean} of target coverage (SMD = − 0.1, 95% CI − 0.57 ~ 0.36, $P = .66$). Actually, in previous studies, researchers concluded that patients with larger breasts size had better sparing OAR when treated in the prone position.[21,27,28,30,35] Montero et al reported that P-FB radiotherapy for patients with larger breasts can effectively reduce D_{mean} of heart by 190cGy ($P = 0.005$) and D_{mean} of ILL by 1051cGy($P = .047$), compared with S-FB.[27] In another study, P-FB can significantly reduce the D_{mean} of the ILL by 270cGy ($P < .001$), the LADCA by 390cGy ($P = .007$) and reduce the D_{mean} of heart by 50cGy($P = .08$) moderately.[30] This is because large size breasts will fold in the supine position, particularly at the inframammary area, which will cause dose inhomogeneity in the target and increase acute and late skin toxicities.[40] It is generally believed that due to the effect of gravity during prone radiotherapy, the dropping breast tissue has a relatively good shape, which can improve the homogeneity of dose in the target area. Moreover, the chest wall obstructed by the treatment bed so that it cannot go down. Hence stretched breast tissue increases the distance between it and the OAR. A concern raised regarding prone breast irradiation is the displacement of the heart anteriorly when prone. Compared to the supine position, researcher found that the mean displacement of the heart was 19 mm anteriorly in prone position ($P < .001$).[41] In patients with small breast size, breast stretching is not obvious when treated in prone position. Therefore, patients with small size breast needed to cautiously decide whether use prone radiotherapy, which may could increase the dose of heart. Interestingly, in recent years, several studies found that prone radiotherapy in patients with small breast size not only can reduce the ILL dose but also reduce the dose of heart and LADCA.[34,38] But in other studies, regardless of breast size, the results have shown that prone position can significantly reduce the dose to ILL but not the heart.[23,25] The first part of our study

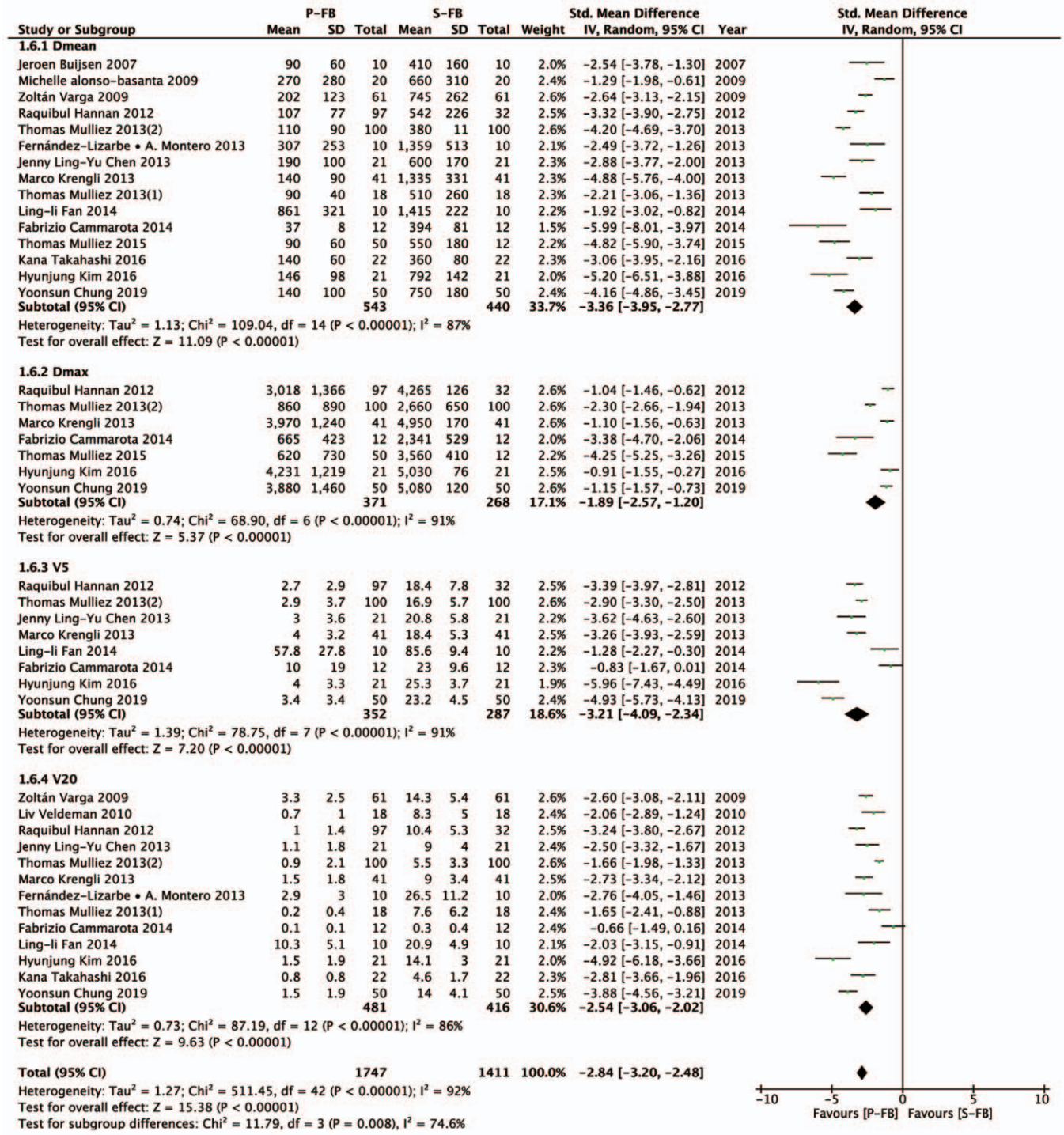

Figure 5. Forest plot of lLL dose between the P-FB group and S-FB group.

also showed that the prone radiotherapy has the advantage of sparing OAR.

In the second part of our research, we found that P-DIBH has better sparing OAR than P-FB and S-DIBH. But due to the lack of evidence, we cannot consider that the above conclusion is necessarily correct. DIBH is an advanced technique through the expanded lung tissue can push the heart away from the chest wall, thereby reducing the dose of the heart. And due to the expansion of lung tissue, the number of alveoli of the same volume irradiated under the same radiotherapy technology is reduced, so that the radiation dose received by the lung tissue is also relatively reduced. Our preliminary a meta-analysis of DIBH versus FB in postoperative radiotherapy for left-side breast cancer[18] had showed that compared with FB group, DIBH group can lower heart dose, LADCA dose and left lung dose more effectively, and the difference was statistically significant (Heart dose, SMD = –

Table 2

The OAR dose of P-FB vs. S-DIBH.

		P-FB			S-DIBH			
OAR	**Studies**	**D_{mean}**	**SD/Min-Max**	**N**	**D_{mean}**	**SD/Min-Max**	**N**	***P* value**
Heart	Mulliez T 2015[33]	250	110	50	220	120	12	<.001
	Saini A S 2018[37]	98	83–115	33	108	120–220	33	.114
LADCA	Mulliez T 2015[33]	830	530	50	1090	780	12	<.001
	Saini A S 2018[37]	657	399–949	33	630	259–798	33	.122
ILL	Mulliez T 2015[33]	90	69	50	500	180	12	<.001
	Saini A S 2018[37]	61	47-80	33	554	429–642	33	<.001

DIBH = Deep inspiration breath hold, FB = Free breathing, ILL = Ipsilateral lung, Max = The maximum value, Min = The minimum value, N = Total number of patients, OAR = Organs at risk, P = Prone, S = Supine. The unit of all D_{mean} data is 'cGy'.

Table 3

The OAR dose of P-DIBH vs. S-DIBH.

		P-DIBH			S-DIBH			
OAR	**Studies**	**D_{mean}**	**SD/Min-Max**	**N**	**D_{mean}**	**SD/Min-Max**	**N**	***P* value**
Heart	Mulliez T 2015[33]	130	30	50	220	120	12	<.001
	Saini A S 2019[39]	77	55–92	25	97	68–123	25	≦.001
LADCA	Mulliez T 2015[33]	330	180	50	1090	780	12	<.001
	Saini A S 2019[39]	349	345–656	25	388	259–798	25	≦.194
ILL	Mulliez T 2015[33]	90	40	50	500	180	12	<.001
	Saini A S 2019[39]	88	62–131	25	541	480–675	25	≦.001

DIBH = Deep inspiration breath hold, FB = Free breathing, ILL = Ipsilateral lung, Max = The maximum value, Min = The minimum value, N = Total number of patients, OAR = Organs at risk, P = Prone, S = Supine. The unit of all D_{mean} data is 'cGy'.

1.36, 95%CI: − 1.64 ~ − 1.09, $P < .01$. LADCA dose, SMD = − 1.45, 95%CI: − 1.62 ~ − 1.27, $P < .01$. Left lung dose, SMD = − 0.52, 95%CI: − 0.81~ − 0.23, $P < .01$). And there was no significant difference in target coverage between the two groups (SMD = 0.03, 95%CI: -0.11~0.18, $P = .64$). Hjelstuen et al reported a decrease in Dmean of heart for patients with left side breast cancers from 6.2 Gy with FB to 3.1 Gy with DIBH. The V20 of heart decreased from 7.8% to 2.3% ($P < .001$), and V40 of heart decreased from 3.4% to 0.3% ($P < .001$).[42] DIBH has shown great advantages in reducing the dose of OAR, whether the combination of DIBH in different positions can bring further dosimetry benefits to patients. In Mulliez's study,[33] they found that reductions in heart D_{mean} with P-DIBH compared to P/S-FB according to breast volume < 750 cc, 750–1500 cc and > 1500 cc were 1.3 (± 0.9 Gy), 0.7 (± 0.7 Gy) and 0.4 (± 0.4 Gy), respectively. The results showed that P-DIBH nearly consistently

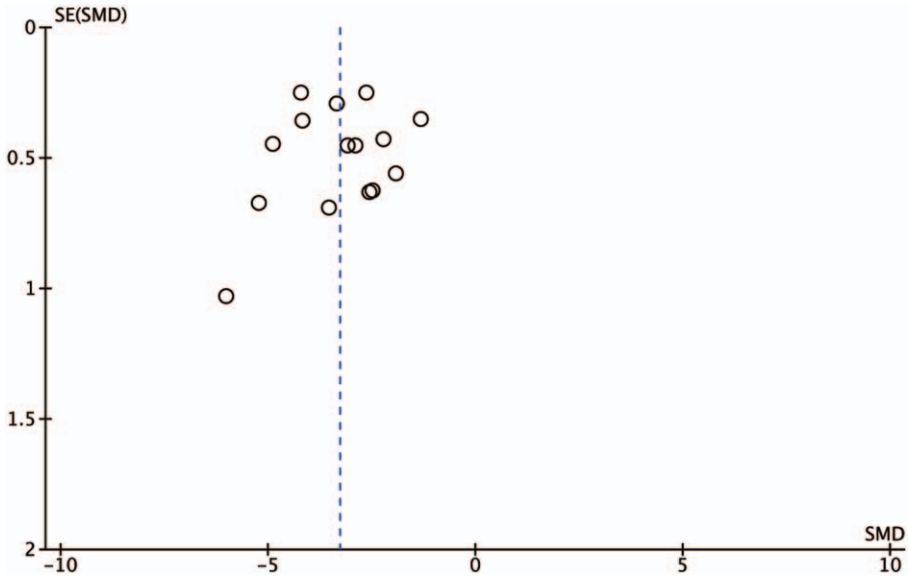

Figure 6. Funnel plot to explore the presence of publication bias.

reduced D_{mean} of heart to less than 2 Gy, regardless of breast volume. Moreover, patients with smaller breast volume seem to benefit the most from P-DIBH. In addition, P-DIBH also can reduce the ILL ($P < .001$) and LADCA dose ($P < .001$). Similarly, Saini et al found that P-DIBH could not only significantly reduce the D_{mean} of ILL ($P \leqq .001$) but also heart ($P \leqq .001$) compared other position combined with different breathing patterns.[39] Hence, patients with large breasts or with small breasts both can benefit from P-DIBH radiotherapy. Combined with the above analysis, P-DIBH might be a good choice for breast cancer patients, especially for patients with small size breasts.

Several limitations of our study should be acknowledged when interpreting the results. First, some heterogeneity was observed in this study due to uncontrolled confounding factors and selection bias. We solved this problem by adopting a random-effects model. Second, only articles published and written in English were included this meta-analysis, which might have resulted in some degree of publication bias. However, no significant publication bias was detected, indicating that no noticeable harm was done by potential publication bias.

Through this meta-analysis of P-FB versus S-FB in postoperative radiotherapy for breast cancer, we found that using P-FB for breast cancer patients allows for a significant reduction in heart dose, LADCA dose, and ILL dose while maintaining D_{mean} of target coverage. Moreover, P-DIBH might become the most promising way for breast cancer patients to undergo radiotherapy. It is worth further exploration by more researchers.

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