

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% Cl $-0.66 \sim -0.36$, P < .00001. LADCA dose, SMD = -0.58, 95% Cl $-0.85 \sim -0.31$, P < .0001. ILL dose, SMD = -2.84, 95% Cl $-3.2 \sim -2.48$, P < .00001). And there was no significant difference in target coverage between the S-FB and P-FB groups (SMD = -0.1, 95% Cl $-0.57 \sim 0.36$, 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, $D_{max} = max \text{ dose}$, $D_{mean} = mean \text{ dose}$, 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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Junming Lai and Fangyan Zhong Junming Lai and Fangyan Zhong contributed equally to this work.

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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 evidencebased 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 40 Gy (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.



However, reporting bias, confounding and baseline differences might be more pronounced cohort studies, as compared to randomized controlled trials. bias may be high. All statistical analyses were conducted using the Cochrane RevMan 5.4 software.

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

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 L	numbers 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.

3.4. LADCA dose

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.

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 $-0.66 \sim -0.36, P < .00001$). D_{mean} (SMD = -0.47, 95% CI $-0.75 \sim -0.19, P = 0.0009$), D_{max} (SMD = -0.57, 95% CI $-0.82 \sim -0.32, P < .00001$), V5 (SMD = -0.40, 95% CI $-0.63 \sim -0.16, P = .001$), V20 (SMD = -0.66, 95% CI $-1.05 \sim -0.26, P = .001$) (Fig. 3).

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 $-0.57 \sim 0.36, P$ = .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

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 $-0.85 \sim -0.31$, P < .0001). D_{mean}

 $\begin{array}{l} (\text{SMD}=-\ 0.58,\ 95\%\ \text{CI}\ -\ 0.85\ \sim\ -\ 0.31,\ P<.0001).\ \text{D}_{\text{mean}} \\ (\text{SMD}=-\ 0.53,\ 95\%\ \text{CI}\ -\ 0.89\ \sim\ -\ 0.16,\ P=.005),\ \text{D}_{\text{max}} \\ (\text{SMD}=-\ 0.80,\ 95\%\ \text{CI}\ -\ 1.52\ \sim\ -\ 0.09,\ P=.03),\ \text{V40} \\ (\text{SMD}=-\ 0.47,\ 95\%\ \text{CI}\ -\ 0.85\ \sim\ -\ 0.09,\ P=.01)\ (\text{Fig. 4}). \end{array}$





		D_CD			C.EP		5	Std Maan Difference		Std Moon Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random. 95% Cl	Year	IV. Random, 95% CI
1.2.1 Dmean										
Michelle alonso-basanta 2009	150	10	12	150	10	12	2 3%	0 00 [-0 80 0 80]	2009	
Zoltán Varga 2009	318	131	34	351	233	34	4 1%	-0.17 [-0.65, 0.30]	2009	
lenny Ling-Yu Chen 2013	390	220	21	370	100	21	3 3%	0 11 [-0 49 0 72]	2013	
Marco Krengli 2013	190	130	17	200	100	17	2.9%	-0.08 [-0.76, 0.59]	2013	
Thomas Mulliez 2013(1)	160	40	12	250	170	12	2 2%	-0 70 [-1 53 0 13]	2013	
Thomas Mulliez 2013(2)	150	60	31	200	110	29	3.8%	-0.56 [-1.08 -0.05]	2013	
Fernández-Lizarbe • A Montero 2013	278	181	10	469	313	10	2.0%	-0.72 [-1.63 0.20]	2013	
Ling-li Fan 2014	1 135	482	10	1 537	403	10	1 0%	-0.79 [-1.71 0.13]	2014	
Thomas Mulliez 2015	220	80	50	400	180	12	2.8%	-1 68 [-2 38 -0 98]	2015	
Hyuniung Kim 2016	276	122	21	414	164	21	2.0%	-0.04 [-1.58 -0.30]	2015	
Kana Takabashi 2016	210	160		200	104	21	1.0%	0.07[0.85 1.00]	2016	
Kana Takanasin 2010	240	120	50	340	260	50	1.9%	0.07 [-0.83, 1.00]	2010	Later Control of Contr
Subtotal (95% CI)	240	120	277	540	300	237	35.0%	-0.37 [-0.77, 0.03]	2019	A
Heterogeneity $Tau^2 = 0.12$; $Chi^2 = 22$	- 36 00	11 /0 -	0.011	2 - E 40	0	237	33.070	-0.47 [-0.73, -0.15]		
Test for overall effects $7 = 2.21 (P = 0.1)$	oo, ur =	11 (P =	0.01);	= 34%						
101 over all effect, z = 5.51 (P = 0.0	1009)									
1.2.2 Dmax										
Raquibul Hannan 2012	3 492	1 229	07	4 116	200	22	4 69	-0 58 [-0 99 -0 17]	2012	
Marco Krepoli 2012	3,462	1,250	17	4,110	000	17	2.0%	-0.36 [-0.39, -0.17]	2012	
Themas Mullion 2012(2)	3,000	1,250	21	4,190	900	21	2.9%	-0.44 [-1.12, 0.24]	2013	
Thomas Mulliez 2015(2)	1 620	000	51	1,210	950	31	3.9%	-0.29 [-0.79, 0.21]	2015	
Huming Kim 2016	1,020	990	50	2,930	1,000	12	2.9%	-1.29 [-1.90, -0.02]	2015	Commence and the second s
Hyunjung Kim 2016	4,921	222	21	5,004	330	21	3.370	-0.27 [-0.88, 0.33]	2016	
Subtotal (95% CI)	4,200	970	266	4,820	680	163	4.0%	-0.66 [-1.07, -0.26]	2019	
	A	/D 0	200	270/		105	22.270	-0.37 [-0.82, -0.32]		×.
Test for overall effect: $Z = 4.52$ (P < 0.0	4, df = 5 00001)	(P = 0.)	23); 1- =	= 27%						
1.2.3 V5										
Marco Krengli 2013	4	4.1	17	4.6	3.9	17	2.9%	-0.15 [-0.82, 0.53]	2013	
Thomas Mulliez 2013(2)	3.8	3.9	31	5.9	5.5	31	3.9%	-0.43 [-0.94, 0.07]	2013	
lenny Ling-Yu Chen 2013	8.8	72	21	8.8	3.9	21	3.3%	0.00 [-0.60, 0.60]	2013	
Hyuniung Kim 2016	7.4	3.7	21	10.7	4.5	21	3.1%	-0.79 [-1.42, -0.16]	2016	
Yoonsun Chung 2019	51	36	50	6.8	35	50	4 7%	-0.48 [-0.87 -0.08]	2019	
Subtotal (95% CI)	3.1	5.0	140	0.0	5.5	140	17.9%	-0.40 [-0.63, -0.16]	2013	•
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.8$	2 df = 4	(P = 0)	43). 12	- 0%						
Test for overall effect: $Z = 3.27$ (P = 0.0	001)	(r = 0.		- 0/6						
1.2.4 V20										
Liv Veldeman 2010	14	14	14	2.4	26	14	2 49	-0.02 [-1.72 -0.14]	2010	
Requibul Hannan 2012	1.4	1.4	14	3.4	2.0	14	2.4%	-0.95 [-1.72, -0.14]	2010	
Marco Kropoli 2012	2.2	3.9	97	2.3	1.8	32	4.7%	-0.03 [-0.43, 0.37]	2012	
Thomas Mullion 2012(1)	1.5	2.2	17	1.5	1.5	17	2.9%	0.00 [-0.07, 0.67]	2013	
Thomas Mullier 2013(1)	0.3	0.1	12	1.9	0.9	12	1.5%	-2.41 [-3.51, -1.32]	2013	
Ling II For 2014	12.0	0.9	31	1.4	2.3	31	3.9%	-0.40 [-0.90, 0.11]	2013	
Ling-II Fan 2014	13.8	8.1	10	20.3	13.1	10	1.8%	-1.10 [-2.05, -0.14]	2014	
Hyunjung Kim 2016	3.4	2.5	21	6.3	3.4	21	3.1%	-0.95 [-1.60, -0.31]	2016	
Subtotal (95% CI)	2.4	2.5	252	3.6	2.4	187	4.7%	-0.49 [-0.88, -0.09] -0.66 [-1.05, -0.26]	2019	•
Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 23$. Test for overall effect: Z = 3.21 (P = 0.0	92, df = 001)	7 (P = 0)	.001);	$ ^2 = 71\%$	13					
Total (95% CI)			935			727	100.0%	-0.51 [-0.66, -0.36]		•
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 59$. Test for overall effect: $Z = 6.61$ (P < 0.0 Test for subgroup differences: $Chi^2 = 1$	84, df = 00001) .68, df =	30 (P =	0.0010	$; ^2 = 5$ $ ^2 = 0\%$	0%				_	-4 -2 0 2 4 Favours [P-FB] Favours [S-FB]
		0 5							0.55	

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 $-3.2 \sim -2.48$, P < .00001). D_{mean} (SMD = -3.36, 95% CI $-3.95 \sim -2.77$, P < .00001), D_{max} (SMD = -1.89, 95% CI $-2.57 \sim -1.2$, P < .00001), V5 (SMD = -3.21, 95% CI $-4.09 \sim -2.34$, P < .00001), V20 (SMD = -2.54, 95% CI $-3.06 \sim -2.02$, 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

		P-FB			S-FB			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.4.1 Dmean										
Thomas Mulliez 2013(2)	540	370	31	930	650	29	6.4%	-0.73 [-1.26, -0.21]	2013	
Marco Krengli 2013	1,180	980	17	1,200	910	17	5.5%	-0.02 [-0.69, 0.65]	2013	
Jenny Ling-Yu Chen 2013	2,090	1,220	21	2,230	810	21	5.9%	-0.13 [-0.74, 0.47]	2013	
Ling-li Fan 2014	2,627	676	10	3,072	716	10	4.3%	-0.61 [-1.51, 0.29]	2014	
Thomas Mulliez 2015	830	530	50	1,760	720	12	5.4%	-1.61 [-2.31, -0.92]	2015	
Hyunjung Kim 2016	1,347	688	21	1,508	671	21	5.9%	-0.23 [-0.84, 0.37]	2016	
Zsuzsanna Kahán 2018	655	603	67	690	386	33	7.0%	-0.06 [-0.48, 0.35]	2018	
Yoonsun Chung 2019	560	380	50	1,000	580	50	7.0%	-0.89 [-1.30, -0.48]	2019	
Subtotal (95% CI)			267			193	47.3%	-0.53 [-0.89, -0.16]		•
Heterogeneity: $Tau^2 = 0.18$	3; Chi ² =	22.42,	df = 7	(P = 0.0)	02); I ²	= 69%				
Test for overall effect: Z =	2.84 (P =	= 0.005)							
1.4.2 Dmax										
Marco Krengli 2013	2,780	1,600	17	3,300	1,320	17	5.5%	-0.35 [-1.02, 0.33]	2013	
Thomas Mulliez 2013(2)	1,950	1,110	31	2,300	1,170	29	6.4%	-0.30 [-0.81, 0.21]	2013	+
Thomas Mulliez 2015	1,290	870	50	3,610	750	12	4.8%	-2.70 [-3.50, -1.90]	2015	
Hyunjung Kim 2016	4,268	1,078	21	4,389	1,041	21	5.9%	-0.11 [-0.72, 0.49]	2016	
Yoonsun Chung 2019	3,090	1,580	50	4,180	1,270	50	7.0%	-0.75 [-1.16, -0.35]	2019	
Subtotal (95% CI)	0.000		169	1.		129	29.6%	-0.80 [-1.52, -0.09]		•
Heterogeneity: $Tau^2 = 0.57$; Chi ² =	31.06,	df = 4	(P < 0.0	00001);	l ² = 87	%			
Test for overall effect: Z =	2.20 (P =	= 0.03)								
1.4.3 V40										
enny Ling-Yu Chen 2013	28	26.1	21	27.9	16.3	21	5.9%	0.00 [-0.60, 0.61]	2013	3
Ling-li Fan 2014	22	12.9	10	31.4	16.3	10	4.3%	-0.61 [-1.51, 0.29]	2014	
Hyunjung Kim 2016	16.9	13.9	21	22.6	15.4	21	5.8%	-0.38 [-0.99, 0.23]	2016	
Yoonsun Chung 2019	5	7.6	50	12.8	11.5	50	7.0%	-0.79 [-1.20, -0.39]	2019	
Subtotal (95% CI)			102			102	23.1%	-0.47 [-0.85, -0.09]		•
Heterogeneity: Tau ² = 0.06	; Chi ² =	4.86, d	If = 3 (I	P = 0.18	$(3); ^2 = 3$	8%				
Test for overall effect: Z =	2.45 (P =	= 0.01)								
Total (95% CI)			538			424	100.0%	-0.58 [-0.85, -0.31]		•
Heterogeneity: $Tau^2 = 0.22$	2; Chi ² =	59.48.	df = 10	5 (P < 0.	.00001)	$ ^2 = 7$	3%		-	
Test for overall effect: Z =	4.26 (P -	< 0.000	1)							-4 -2 0 2
	CI .2	0.00	15 .	10 0	721 12	00/				ravours [P-FB] Favours [S-FB]

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 \sim - 0.36, P < .00001), LADCA (MD=- 0.58, 95% CI - 0.85 \sim - 0.31, P < .0001) and ILL (SMD=- 2.84, 95% CI - 3.2 \sim - 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 \sim 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

		P-FR			-FR			Std Mean Difference		Std Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% Cl
1.6.1 Dmean										
Jeroen Buijsen 2007	90	60	10	410	160	10	2.0%	-2.54 [-3.78, -1.30]	2007	
Michelle alonso-basanta 2009	270	280	20	660	310	20	2.4%	-1.29 [-1.98, -0.61]	2009	
Zoltán Varga 2009	202	123	61	745	262	61	2.6%	-2.64 [-3.13, -2.15]	2009	-
Raquibul Hannan 2012	107	77	97	542	226	32	2.5%	-3.32 [-3.90, -2.75]	2012	-
Thomas Mulliez 2013(2)	110	90	100	380	11	100	2.6%	-4.20 [-4.69, -3.70]	2013	-
Fernández-Lizarbe • A. Montero 2013	307	253	10	1,359	513	10	2.1%	-2.49 [-3.72, -1.26]	2013	
Jenny Ling-Yu Chen 2013	190	100	21	600	170	21	2.3%	-2.88 [-3.77, -2.00]	2013	
Marco Krengli 2013	140	90	41	1,335	331	41	2.3%	-4.88 [-5.76, -4.00]	2013	
Thomas Mulliez 2013(1)	90	40	18	510	260	18	2.3%	-2.21 [-3.06, -1.36]	2013	
Ling-li Fan 2014	861	321	10	1,415	222	10	2.2%	-1.92 [-3.02, -0.82]	2014	
Fabrizio Cammarota 2014	37	8	12	394	81	12	1.5%	-5.99 [-8.01, -3.97]	2014	
Thomas Mulliez 2015	90	60	50	550	180	12	2.2%	-4.82 [-5.90, -3.74]	2015	
Kana Takahashi 2016	140	60	22	360	80	22	2.3%	-3.06 [-3.95, -2.16]	2016	and the second se
Hyunjung Kim 2016	146	98	21	792	142	21	2.0%	-5.20 [-6.51, -3.88]	2016	
Subtotal (95% CI)	140	100	543	750	180	440	33.7%	-4.16 [-4.86, -3.45]	2019	
Heterogeneity: $Tau^2 = 1.13$; $Chi^2 = 109$ Test for overall effect: Z = 11.09 (P < 0	.04, df = .00001)	= 14 (P -	< 0.000	01); I ² =	= 87%					
1.6.2 Dmax										
Raquibul Hannan 2012	3,018	1,366	97	4,265	126	32	2.6%	-1.04 [-1.46, -0.62]	2012	
Thomas Mulliez 2013(2)	860	890	100	2,660	650	100	2.6%	-2.30 [-2.66, -1.94]	2013	-
Marco Krengli 2013	3,970	1,240	41	4,950	170	41	2.6%	-1.10 [-1.56, -0.63]	2013	
Fabrizio Cammarota 2014	665	423	12	2,341	529	12	2.0%	-3.38 [-4.70, -2.06]	2014	
Thomas Mulliez 2015	620	730	50	3,560	410	12	2.2%	-4.25 [-5.25, -3.26]	2015	
Hyunjung Kim 2016	4,231	1,219	21	5,030	76	21	2.5%	-0.91 [-1.55, -0.27]	2016	
Yoonsun Chung 2019	3,880	1,460	50	5,080	120	50	2.6%	-1.15 [-1.57, -0.73]	2019	_
Subtotal (95% Cl) Heterogeneity: $Tau^2 = 0.74$; $Chi^2 = 68.9$	90, df =	6 (P < 0	371).00001	.); I ² = 9	1%	268	17.1%	-1.89 [-2.57, -1.20]		•
Test for overall effect: $Z = 5.37$ (P < 0.0	00001)									
1.6.3 V5								12521 2010 - 12522		
Raquibul Hannan 2012	2.7	2.9	97	18.4	7.8	32	2.5%	-3.39 [-3.97, -2.81]	2012	-
Thomas Mulliez 2013(2)	2.9	3.7	100	16.9	5.7	100	2.6%	-2.90 [-3.30, -2.50]	2013	
Jenny Ling-Yu Chen 2013	3	3.6	21	20.8	5.8	21	2.2%	-3.62 [-4.63, -2.60]	2013	
Marco Krengli 2013	4	3.2	41	18.4	5.3	41	2.5%	-3.26 [-3.93, -2.59]	2013	
Ling-li Fan 2014	57.8	27.8	10	85.6	9.4	10	2.2%	-1.28 [-2.27, -0.30]	2014	
Fabrizio Cammarota 2014	10	19	12	23	9.6	12	2.3%	-0.83 [-1.67, 0.01]	2014	
Hyunjung Kim 2016	4	3.3	21	25.3	3.7	21	1.9%	-5.96 [-7.43, -4.49]	2016	
Yoonsun Chung 2019 Subtotal (95% CI)	3.4	3.4	352	23.2	4.5	50	2.4%	-4.93 [-5.73, -4.13]	2019	-
Heterogeneity: $Tau^2 = 1.39$; $Chi^2 = 78.3$	75, df =	7 (P < 0	0.00001); ² = 9	1%	207	10.0%	-3.21 [-4.09, -2.34]		•
Test for overall effect: $Z = 7.20$ (P < 0.0	00001)									
1.6.4 V20										
Zoltán Varga 2009	3.3	2.5	61	14.3	5.4	61	2.6%	-2.60 [-3.08, -2.11]	2009	-
Liv Veldeman 2010	0.7	1	18	8.3	5	18	2.4%	-2.06 [-2.89, -1.24]	2010	
Raquibul Hannan 2012	1	1.4	97	10.4	5.3	32	2.5%	-3.24 [-3.80, -2.67]	2012	-
Jenny Ling-Yu Chen 2013	1.1	1.8	21	9	4	21	2.4%	-2.50 [-3.32, -1.67]	2013	
Thomas Mulliez 2013(2)	0.9	2.1	100	5.5	3.3	100	2.6%	-1.66 [-1.98, -1.33]	2013	-
Marco Krengli 2013	1.5	1.8	41	9	3.4	41	2.5%	-2.73 [-3.34, -2.12]	2013	
Fernández-Lizarbe • A. Montero 2013	2.9	3	10	26.5	11.2	10	2.0%	-2.76 [-4.05, -1.46]	2013	
Thomas Mulliez 2013(1)	0.2	0.4	18	7.6	6.2	18	2.4%	-1.65 [-2.41, -0.88]	2013	
Fabrizio Cammarota 2014	0.1	0.1	12	0.3	0.4	12	2.4%	-0.66 [-1.49, 0.16]	2014	
Ling-li Fan 2014	10.3	5.1	10	20.9	4.9	10	2.1%	-2.03 [-3.15, -0.91]	2014	
Hyunjung Kim 2016	1.5	1.9	21	14.1	3	21	2.0%	-4.92 [-6.18, -3.66]	2016	
Kana Takahashi 2016	0.8	0.8	22	4.6	1.7	22	2.3%	-2.81 [-3.66, -1.96]	2016	
Yoonsun Chung 2019	1.5	1.9	50	14	4.1	50	2.5%	-3.88 [-4.56, -3.21]	2019	-
Subtotal (95% CI) Heterogeneity: Tau ² = 0.73; Chi ² = 87.1 Test for overall effect: $7 = 9.63$ (P < 0.0	19, df =	12 (P <	481	(1); $I^2 =$	86%	416	30.6%	-2.54 [-3.06, -2.02]		
Total (05% CI)	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		1747			1411	100.0%	-2 84 [-2 20 - 2 48]		
Heterogeneity: Tau ² - 1 27: Chi ² - 511	45 df -	42 (P	1/4/	01) 12	- 97%	1411	100.0%	-2.04 [-3.20, -2.48]	+	
Test for overall effect: $Z = 1.27$; Chi ⁺ = 511 Test for overall effect: $Z = 15.38$ (P < 0 Test for subgroup differences: Chi ² = 1	.45, df = .00001) 1.79, df	= 42 (P =	= 0.008	$(01); 1^2 = 7$	4.6%				-1	0 -5 0 5 Favours [P-FB] Favours [S-FB]
	Fiau	re 5.	Forest	plot of	ILL (dose b	etween 1	the P-FB group and	S-FB aro	up.

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					
OAR	Studies	D _{mean}	SD/Min-Max	Ν	D _{mean}	SD/Min-Max	Ν	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					
OAR	Studies	D _{mean}	SD/Min-Max	Ν	D _{mean}	SD/Min-Max	Ν	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	
	Saini A S 2019 ^[39]	88	62–131	25	541	480–675	25	≦.001

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

1.36, 95%CI: $-1.64 \sim -1.09$, P < .01. LADCA dose, SMD = -1.45, 95%CI: $-1.62 \sim -1.27$, P < .01. Left lung dose, SMD = -0.52, 95%CI: $-0.81 \sim -0.23$, P < .01). And there was no significant difference in target coverage between the two groups (SMD=0.03, 95%CI: $-0.11 \sim 0.18$, 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 (\pm 0.9 Gy), 0.7 (\pm 0.7 Gy) and 0.4 (\pm 0.4 Gy), respectively. The results showed that P-DIBH nearly consistently



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 ($P \le .001$) but also heart ($P \le .001$) 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.

Author contributions

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References

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
- [2] Cuzick J, Stewart H, Rutqvist L, et al. Cause-specific mortality in longterm survivors of breast cancer who participated in trials of radiotherapy. J Clin Oncol 1994;12:447–53.
- [3] (EBCTCG) EBCTCGEffects 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: 2087–106.
- [4] EBCTCG) EBCTCGFavourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Lancet 2000;355:1757–70.
- [5] Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233–41.
- [6] Henson KE, McGale P, Taylor C, Darby SC. Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer. Br J Cancer 2013;108:179–82.

- [7] Taylor CW, Povall JM, McGale P, et al. Cardiac dose from tangential breast cancer radiotherapy in the year 2006. Int J Radiat Oncol Biol Phys 2008;72:501–7.
- [8] Nilsson G, Holmberg L, Garmo H, et al. Distribution of coronary artery stenosis after radiation for breast cancer. J Clin Oncol 2012;30:380–6.
- [9] Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013;368: 987–98.
- [10] Gagliardi G, Bjöhle J, Lax I, et al. Radiation pneumonitis after breast cancer irradiation: analysis of the complication probability using the relative seriality model. Int J Radiation Oncology Biol Phys 2000;46:373–81.
- [11] Grantzau T, Thomsen MS, Vaeth M, et al. Risk of second primary lung cancer in women after radiotherapy for breast cancer. Radiother Oncol 2014;111:366–73.
- [12] Schubert LK, Gondi V, Sengbusch E, et al. Dosimetric comparison of leftsided whole breast irradiation with 3DCRT, forward-planned IMRT, inverse-planned IMRT, helical tomotherapy, and topotherapy. Radiother Oncol 2011;100:241–6.
- [13] Yin Y, Chen J, Sun T, et al. Dosimetric research on intensity-modulated arc radiotherapy planning for left breast cancer after breast-preservation surgery. Med Dosim 2012;37:287–92.
- [14] Muren LP, Maurstad G, Hafslund R, et al. Cardiac and pulmonary doses and complication probabilities in standard and conformal tangential irradiation in conservative management of breast cancer. Radiother Oncol 2002;62:173–83.
- [15] Iorio GC, Franco P, Gallio E, et al. Volumetric modulated arc therapy (VMAT) to deliver nodal irradiation in breast cancer patients. Med Oncol 2017;35:1–8.
- [16] Ares C, Khan S, Macartain AM, et al. Postoperative proton radiotherapy for localized and locoregional breast cancer: potential for clinically relevant improvements? Int J Radiat Oncol Biol Phys 2010;76:685–97.
- [17] Bergom C, Currey A, Desai N, Tai A, Strauss JB. Deep inspiration breath hold: techniques and advantages for cardiac sparing during breast cancer irradiation. Front Oncol 2018;8:87–96.
- [18] Lai J, Hu S, Luo Y, et al. Meta-analysis of deep inspiration breath hold (DIBH) versus free breathing (FB) in postoperative radiotherapy for leftside breast cancer. Breast Cancer 2020;27:299–307.
- [19] White R, Foroudi F, Sia J, Marr MA, Lim Joon D. Reduced dose to small bowel with the prone position and a belly board versus the supine position in neoadjuvant 3D conformal radiotherapy for rectal adenocarcinoma. J Med Radiat Sci 2017;64:120–4.
- [20] Scobioala S, Kittel C, Niermann P, et al. A treatment planning study of prone vs. supine positions for locally advanced rectal carcinoma: comparison of 3dimensional conformal radiotherapy, tomotherapy, volumetric modulated arc therapy, and intensity-modulated radiotherapy. Strahlenther Onkol 2018;194:975–84.
- [21] Buijsen J, Jager JJ, Bovendeerd J, et al. Prone breast irradiation for pendulous breasts. Radiother Oncol 2007;82:337–40.
- [22] Alonso-Basanta M, Ko J, Babcock M, Dewyngaert JK, Formenti SC. Coverage of axillary lymph nodes in supine vs. prone breast radiotherapy. Int J Radiat Oncol Biol Phys 2009;73:745–51.
- [23] Varga Z, Hideghety K, Mezo T, et al. Individual positioning: a comparative study of adjuvant breast radiotherapy in the prone versus supine position. Int J Radiat Oncol Biol Phys 2009;75:94–100.
- [24] Veldeman L, Speleers B, Bakker M, et al. Preliminary results on setup precision of prone-lateral patient positioning for whole breast irradiation. Int J Radiat Oncol Biol Phys 2010;78:111–8.
- [25] Hannan R, Thompson RF, Chen Y, et al. Hypofractionated whole-breast radiation therapy: does breast size matter? Int J Radiat Oncol Biol Phys 2012;84:894–901.
- [26] Chen JL, Cheng JC, Kuo SH, Chan HM, Huang YS, Chen YH. Prone breast forward intensity-modulated radiotherapy for Asian women with early left breast cancer: factors for cardiac sparing and clinical outcomes. J Radiat Res 2013;54:899–908.
- [27] Fernandez-Lizarbe E, Montero A, Polo A, et al. Pilot study of feasibility and dosimetric comparison of prone versus supine breast radiotherapy. Clin Transl Oncol 2013;15:450–9.
- [28] Krengli M, Masini L, Caltavuturo T, et al. Prone versus supine position for adjuvant breast radiotherapy: a prospective study in patients with pendulous breasts. Radiation Oncol 2013;8:232–7.
- [29] Mulliez T, Speleers B, Madani I, et al. Whole breast radiotherapy in prone and supine position: is there a place for multi-beam IMRT? Radiation Oncol 2013;8:151–6.

- [30] Mulliez T, Veldeman L, van Greveling A, et al. Hypofractionated whole breast irradiation for patients with large breasts: a randomized trial comparing prone and supine positions. Radiother Oncol 2013;108: 203–8.
- [31] Cammarota F, Giugliano FM, Iadanza L, et al. Hypofractionated breast cancer radiotherapy. Helical tomotherapy in supine position or classic 3D- conformal radiotherapy in prone position: which is better? Anticancer Res 2014;34:1233–8.
- [32] Fan LL, Luo YK, Xu JH, He L, Wang J, Du XB. A dosimetry study precisely outlining the heart substructure of left breast cancer patients using intensity-modulated radiation therapy. J Appl Clin Med Phys 2014;15:4624–34.
- [33] Mulliez T, Veldeman L, Speleers B, et al. Heart dose reduction by prone deep inspiration breath hold in left-sided breast irradiation. Radiother Oncol 2015;114:79–84.
- [34] Kim H, Kim J. Evaluation of the anatomical parameters for normal tissue sparing in the prone position radiotherapy with small sized left breasts. Oncotarget 2016;7:72211–8.
- [35] Takahashi K, Morota M, Kagami Y, et al. Prospective study of postoperative whole breast radiotherapy for Japanese large-breasted women: a clinical and dosimetric comparisons between supine and prone positions and a dose measurement using a breast phantom. BMC Cancer 2016;16:757–67.

- [36] Kahan Z, Rarosi F, Gaal S, et al. A simple clinical method for predicting the benefit of prone vs. supine positioning in reducing heart exposure during left breast radiotherapy. Radiother Oncol 2018;126:487–92.
- [37] 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;19:195–204.
- [38] Chung Y, Yu JI, Park W, Choi DH. Phase II study, feasibility of prone position in postoperative whole breast radiotherapy: a dosimetric comparison. Cancer Res Treat 2019;51:1370–9.
- [39] Saini AS, Das IJ, Hwang CS, Biagioli MC, Lee WE. Biological indices evaluation of various treatment techniques for left-sided breast treatment. Pract Radiat Oncol 2019;9:e579–90.
- [40] Bentel GC, Marks LB, Whiddon CS, Prosnitz LR. Acute and late morbidity of using a breast positioning ring in women with large/ pendulous breasts. Radiother Oncol 1999;50:277–81.
- [41] Chino JP, Marks LB. Prone positioning causes the heart to be displaced anteriorly within the thorax: implications for breast cancer treatment. Int J Radiat Oncol Biol 2008;70:916–20.
- [42] Hjelstuen MHB, Mjaaland I, Vikström J, Dybvik KI. Radiation during deep inspiration allows loco-regional treatment of left breast and axillary-, supraclavicular- and internal mammary lymph nodes without compromising target coverage or dose restrictions to organs at risk. Acta Oncol 2011;51:333–44.