

Review Article

# Comparison of organs at risk doses between deep inspiration breath-hold and free-breathing techniques during radiotherapy of left-sided breast cancer: A Meta-Analysis

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## Abstract

After radiotherapy (RT) of left-sided breast cancer patients, organs at risk (OARs) such as heart, left anterior descending (LAD) coronary artery, and left lung could be affected by radiation dose in the long term. The objective of this study was to perform a comprehensive meta-analysis and determine OARs dose reduction during left-sided breast cancer treatment using different RT modalities combined with deep inspiration breath-hold (DIBH) relative to free-breathing (FB). PubMed, Scopus, EMBASE, ProQuest, Google Scholar, and Cochrane Library electronic databases were used to search for studies until June 6, 2021. Nineteen eligible studies were selected and analyzed using the RevMan 5.3 statistical software package. The pooled weighted mean difference (MD) with their 95% confidence intervals for each of the three OAR mean doses were determined using a random-effects meta-analysis model to assess the dose reductions. From a total of 189 studies, 1 prospective study, 15 retrospective studies, and 3 randomized control trials (RCTs) with an overall of 634 patients were included. Reduction of doses to the heart (weighted MD = -1.79 Gy; 95% CI (-2.28, -1.30); P = 0.00001), LAD (weighted MD = -8.34 Gy; 95% CI (-11.06, -5.61); P = 0.00001), and left-lung (weighted MD = -0.90 Gy; 95% CI (-1.19, -0.61); P = 0.00001) were observed using DIBH combinations relative to FB combination. This study emphasizes that during the treatment of left-sided breast/chest wall (CW) ± supraclavicular (SCV) ± infraclavicular (ICV) ± internal mammary chain (IMC) lymph nodes (LN) ± axillary (Ax)/ cancer patients, different RT modalities combined with DIBH techniques are better options to reduce dose to OARs compared to FB, which benefits to minimize the long-term complications.

**Keywords:** radiotherapy; organs at risk; left-side breast cancer; deep inspiration breath-hold.

## Introduction

Based on the global burden of cancers reported by GLOBOCAN 2018, the primary cause of cancer death among females is breast cancer.<sup>1,2</sup> Anatomically, the heart is closer to the left side of the breast than the right side.<sup>3</sup> Left anterior descending (LAD) and left-lung are anterior to the heart and close to the chest wall (CW).<sup>4,5</sup> Radiotherapy (RT) is an essential multidisciplinary type of cancer treatment and used to damage the Deoxyribonucleic acid (DNA) of the left-sided breast/CW ± supraclavicular (SCV) ± infraclavicular (ICV) ± internal mammary chain (IMC) lymph nodes (LN) ± axillary (Ax)/ of cancer cells.<sup>6-8</sup> Despite its benefits, RT can increase non-cancer-

specific mortality due to its effect on the heart, LAD, and left-lung after irradiating left-side breast cancer.<sup>9,10</sup> After five or more years of RT to the left-sided breast cancer patients, the risk of secondary left-lung cancer and heart disease increased linearly at 8.5% per 1 Gray (Gy) and 7.4% per 1 Gy mean doses respectively, with no minimum threshold dose.<sup>11,12</sup> Recently, after more than 0.1 years of follow-up, van den Bogaard et al. showed the acute coronary events' cumulative incidence increased linearly by 16.5% per 1 Gy.<sup>13</sup>

The free-breathing (FB) technique consists of the irradiation of the tumor for every possible position during the respiratory cycle.<sup>14</sup> The disadvantage of the FB technique is that it is difficult to achieve an adequate balance between covering the

tumor by the shaped beams and minimizing the impact of exposure to OARs when there is a significant anatomical challenge (e.g. the presence of a tissue expander or a permanent breast implant). In such situations, FB techniques place the heart, lungs, contralateral breast, as well as the rest of the normal tissue at risk of unnecessary high dose exposure, which should be minimized.<sup>15</sup> Respiratory motion compensation and mitigation techniques are required to apply in treatment plans and decrease uncertainties in dose delivery by maintaining target dose coverage.<sup>16</sup> During the treatment of left-sided breast cancer patients, some of the techniques commonly employed to reduce the dose to OAR structures while maintaining the dose coverage to the target volume are using deep inspiration breath-hold (DIBH) techniques, setting the patient in the prone position, and irradiating the tumor bed after removing a neoplastic mass through a surgical operation. Moreover, the RT modalities commonly used are intensity-modulated RT (IMRT), volumetric modulated arc therapy (VMAT), and proton beam therapy (PBT).<sup>17,18</sup> There are two different DIBH techniques in routine clinical practice: voluntary DIBH (vDIBH) and computer-controlled (moderate) DIBH are available and implemented to deliver dose during specific portions of the respiratory cycle. These techniques significantly vary concerning additional equipment required, patient feedback systems (surface-based (tracking with or without markers), spirometry-based, room-lasers, and DIBH stick), intra-fractional monitoring systems, and utilized devices. Generally, to achieve DIBH, repeating the breath-hold voluntarily and controlling the respiratory cycle or using commercially available machines that are computer-controlled devices that can support DIBH through feedback

approaches, airway blocking, or both are needed.<sup>19,20</sup> The combined use of different RT modalities with DIBH techniques during the treatment of left-sided breast cancer patients can spare the heart, LAD, and left-lung by pushing the target far from the heart or moving the heart far down from the radiation field. Thus, the separation between the heart and breast using the expansion of the left lung and flattening of the diaphragm becomes wider.<sup>21,22</sup> Based on the positional reproducibility and ability to spare OARs, the two DIBH techniques are comparable.<sup>23</sup> The focus of this study was to perform a meta-analysis and determine the significance of the combined use of different RT modalities with DIBH techniques in reducing OARs doses compared to FB combinations.

## Methods and Materials

The analyses of this study were done based on the existing literature. Thus, no ethical approval was needed as it did not involve using patients' data. Moreover, PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting method for the results of studies was used.<sup>24</sup>

## Search strategy

A comprehensive search of relevant studies published in English until June 6, 2021, was done using PubMed, EMBASE, Scopus, Cochrane Library, ProQuest, and Google Scholar databases. A core strategy was initially developed in PubMed and then translated to each database. The main keywords used for the search in the main body of the text are presented in **Table 1**.

**Table 1. The main keywords used for the search in the body of the text**

| Search Item                  | Search Terms (Free text terms and MeSH terms)                                                                                                                                                                                                                                                                                                                               |
|------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| left-side breast cancer      | (unilateral breast neoplasms"[MeSH Terms] OR "unilateral breast neoplasms" OR "left-side breast cancer" OR ((unilateral OR Left-handed) AND ("mammary glands, human"[MeSH Terms] OR "mammary" OR "breast"[MeSH Terms] OR "breast")) AND ("neoplasms"[MeSH Terms] OR "neoplasms" OR "cancer" OR "tumour" OR "tumor" OR malignant OR "carcinoma"[MeSH Terms] OR "carcinoma")) |
| deep inspiration breath-hold | ("breath-holding"[MeSH Terms] OR "breath-holding" OR "respiratory-motion monitoring" OR "respiratory motion management" OR "respiratory motion control" OR "deep inspiration breath-hold" OR "Voluntary breath-hold")                                                                                                                                                       |
| radiotherapy                 | ("radiotherapy" OR "radiotherapy"[MeSH Terms] OR "radiation therapy" OR "radiation treatment" OR "irradiation")                                                                                                                                                                                                                                                             |
| dose reduction               | (dose reduce OR dose reduced OR dose reduces OR dose reducing OR dose reduction OR dose reductions)                                                                                                                                                                                                                                                                         |
| organs at risk               | ("organs at risk"[MeSH Terms] OR "organs at risk" OR OAR OR "heart"[MeSH Terms] OR "heart" OR "lung"[MeSH Terms] OR "lung" OR left anterior descending coronary artery[MeSH Terms] OR "LAD")                                                                                                                                                                                |
| study design                 | ("randomized controlled trials" OR randomized controlled trials [MeSH Terms] OR "retrospective studies"[MeSH Terms] OR "retrospective studies" OR "retrospective study" OR "prospective studies"[MeSH Terms] OR "prospective studies" OR "prospective study" OR clinical trials[MeSH Terms] OR trials OR "clinical trials" OR trial OR outcome)                             |

Field = All fields. Abbreviation: MeSH, Medical Subject Headings; OAR, organs at risk; LAD, left anterior descending coronary artery

## Studies exclusion and inclusion criteria

After duplications were removed from the imported studies, the remaining studies were further screened using different criteria. We included eligible studies if they met the following criteria: (i) studies from prospective, retrospective, and RCTs designs; (ii) studies reported comparisons of mean absorbed doses in the heart, LAD, and left-lung during the treatment of left-sided breast cancer patients using different RT modalities combined with both DIBH and FB techniques; (iii) studies about left-side female breast cancer RT; (iv) studies with most details and recently published if the patient data appeared in more than one study. We excluded ineligible studies if they met the following criteria: (i) studies which were not likely dose comparisons on heart, LAD, and left-lung; (ii) studies which were reviews and meta-analysis, abstracts, case reports, and lectures; (iii) studies which cannot provide sufficient and qualified data; (iv) studies which were about right-sided female breast RT; (v) studies which were not about humans; (vi) studies which were about male breast RT; (vii) studies of unreported sample size, mean dose with a standard deviation or 95% confidence interval (CI). Finally, 19 studies were identified that met the selection criteria.

## Extraction of data from the studies

From the 19 included studies, the relevant outcome data related to the heart, LAD, and left-lung during left-sided breast cancer RT combined with DIBH and FB techniques were extracted. The extracted data from each study were: the name of the first author and year of publication, country, design of the study, period of the study, RT techniques used in the study, total dose (Gy)/fractions, sample size (number of left-sided female breast cancer patients (N) who underwent RT), age, mean absorbed doses to

OAR (the heart, LAD, and left-lung calculated using alpha/beta and 2 Gy equivalent), the standard difference (SD), DIBH technique, and treated area.

## Quality assessment of the studies

Different study designs: prospective, retrospective, and RCTs were applied to study the 19 included eligible studies. In this study, we used two types of quality assessment tools for both non-randomized and randomized study designs: Newcastle-Ottawa Scale (NOS) and Cochrane collaboration's risk of bias. Newcastle-Ottawa Scale (NOS) quality assessment scale was applied to assess the quality of non-randomized studies such as prospective and retrospective.<sup>33</sup> Cochrane collaboration's risk of bias tool was used to evaluate the quality of the RCTs.<sup>34</sup> NOS established nine points criteria to assess the quality of each cohort study: four points for the quality of selection, two points for comparability, and three points for the quality of the outcome. These nine points criteria were: representativeness of exposed cohort, selection of non-exposed cohort, ascertainment of exposure, a demonstration that result of interest was not present at the start of the study, adjust for the most critical risk factor, adjust for other risk factors, assessment of outcome, follow-up long enough for results to occur, and adequacy of follow up of cohorts. **Table 2** shows detail of the NOS tool. Cochrane collaboration's risk of bias tool has also established seven points criteria to evaluate the quality of each RCT study: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, results of selective reporting, and other sources of bias. **Figure 1** shows detail of this tool.

**Table 2. The sixteen non-randomized studies quality assessment using the Newcastle-Ottawa scale. First author of the study is represented from the author, publication column. I Representativeness of exposed cohort, II Selection of non-exposed cohort, III Ascertainment of exposure, IV Demonstration that outcome of interest was not present at start of study, V Adjust for the most important risk factor, VI Adjust for other risk factors, VII Assessment of outcome, VIII Follow-up long enough for outcomes to occur, IX Adequacy of follow up of cohorts.**

| Author, publication year        | Selection |    |     |    | Comparability |    | Outcome |      |    | Total quality score |
|---------------------------------|-----------|----|-----|----|---------------|----|---------|------|----|---------------------|
|                                 | I         | II | III | IV | V             | VI | VII     | VIII | IX |                     |
| Aiello <sup>29</sup> , 2019     | 1         | 1  | 1   | 1  | 1             | 1  | 0       | 1    | 0  | 7                   |
| Al-Hammadi <sup>30</sup> , 2018 | 1         | 1  | 1   | 1  | 1             | 1  | 0       | 1    | 0  | 7                   |
| Cao <sup>21</sup> , 2019        | 1         | 1  | 0   | 1  | 1             | 1  | 0       | 1    | 1  | 7                   |
| Joo <sup>33</sup> , 2015        | 1         | 1  | 1   | 1  | 1             | 1  | 0       | 1    | 0  | 7                   |
| Kathpal <sup>34</sup> , 2016    | 1         | 1  | 1   | 1  | 1             | 1  | 0       | 1    | 0  | 7                   |
| Kim <sup>35</sup> , 2018        | 1         | 1  | 1   | 1  | 1             | 1  | 0       | 1    | 0  | 7                   |
| Lawler <sup>3</sup> , 2017      | 1         | 1  | 0   | 0  | 1             | 1  | 0       | 1    | 1  | 6                   |
| Mathieu <sup>36</sup> , 2020    | 1         | 1  | 1   | 1  | 1             | 1  | 0       | 1    | 0  | 7                   |
| Nguyen <sup>37</sup> , 2018     | 0         | 1  | 1   | 0  | 1             | 1  | 0       | 1    | 1  | 6                   |
| Oechsner <sup>38</sup> , 2019   | 0         | 1  | 1   | 0  | 1             | 1  | 0       | 1    | 1  | 6                   |
| Rochet <sup>40</sup> , 2015     | 0         | 1  | 1   | 0  | 1             | 1  | 0       | 1    | 1  | 6                   |
| Sakka <sup>41</sup> , 2017      | 1         | 1  | 1   | 1  | 1             | 1  | 0       | 1    | 0  | 7                   |
| Sripathi <sup>42</sup> , 2017   | 0         | 1  | 1   | 1  | 1             | 1  | 0       | 1    | 1  | 7                   |
| Tamburella <sup>43</sup> , 2017 | 0         | 1  | 1   | 0  | 1             | 1  | 0       | 1    | 1  | 6                   |
| Wiant <sup>44</sup> , 2015      | 0         | 1  | 1   | 0  | 1             | 1  | 0       | 1    | 1  | 6                   |
| Yeung <sup>45</sup> , 2015      | 1         | 1  | 1   | 0  | 1             | 1  | 0       | 1    | 1  | 7                   |

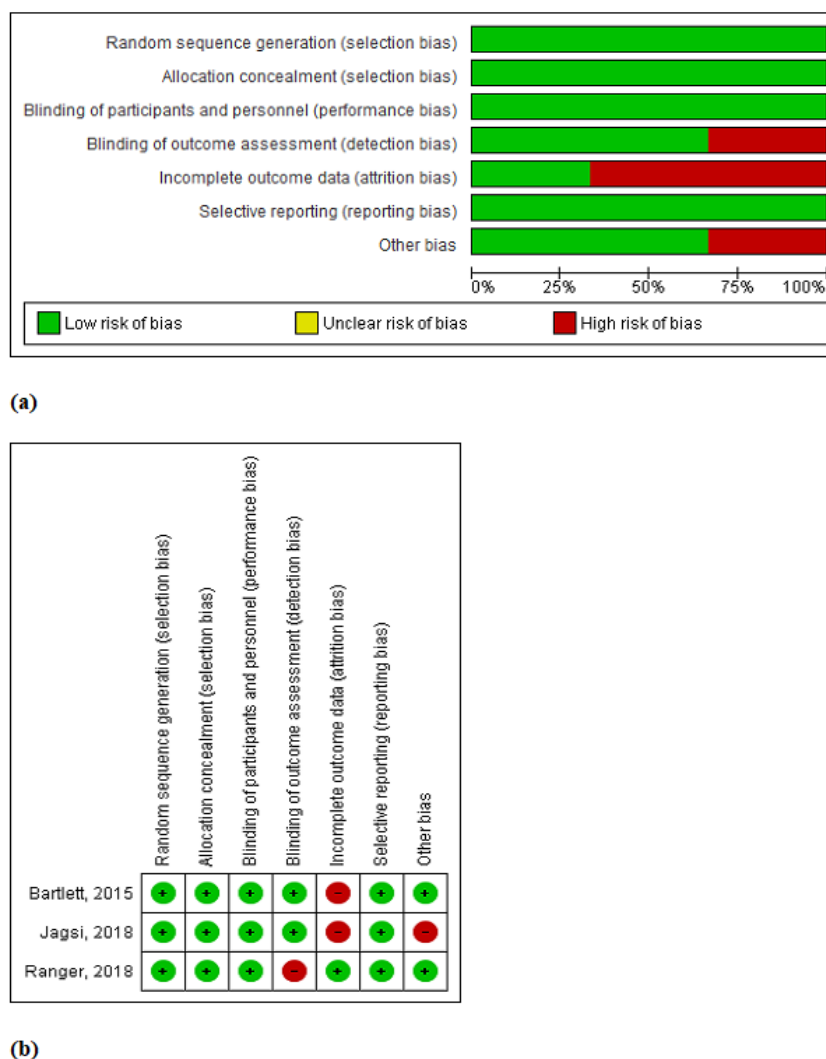


**Figure 1. The three randomized control trials (RCTs) studies using quality assessment the Cochrane collaboration's risk of bias tool (a) Risk of bias graph. (b) Risk of bias summary. Low risk of bias (+), high risk of bias (-).**

### Statistical analysis of the studies

The Cochrane Collaboration statistical software package known as RevMan 5.3 was applied to analyze the data extracted from the included studies. The weighted mean difference (MD) of radiation dose has greater statistical power and is clinically more interpretable than the standardized mean difference (SMD).<sup>25</sup> Weighted MD is used to compute an absolute measure and is created by pooling the results of studies that have used the same outcome measure in a manner that weights the results of each study by the size of the sample. The weighted MD is readily interpretable because it is on the same measurement scale as the clinical outcome measure.<sup>26</sup> The mean absorbed doses to the heart, LAD, and left-lung from the RT combined with DIBH and FB were compared using the weighted MD with their 95% confidence intervals (95% CI). A random-effects meta-analysis model was used to estimate the overall pooled weighted MD in case of high heterogeneity, whereas a fixed-effects meta-analysis model was used in case of low heterogeneity between studies.

The significant heterogeneous nature found in the weighted MD of the included studies was evaluated by considering a chi-square-based Q-test with a  $p < 0.1$  significance level and  $> 50\%$   $I^2$  statistical value. Moreover, funnel plots were used to investigate the existence of publication bias. Funnel plots are a visual tool for investigating publication and other biases in meta-analysis. They are simple scatterplots of the effects estimated from individual studies (horizontal axis) against a measure of study size (vertical axis). The name "funnel plot" is based on the precision in estimating the underlying effect increasing as the sample size of component studies increases. Therefore, in the absence of bias, results from small studies will scatter widely at the bottom of the graph, with the spread narrowing among more extensive studies. Publication bias (the association of publication probability with the statistical significance of study results) may lead to asymmetrical funnel plots.<sup>27</sup>

## Results

### Search results with study characteristics

A total of 189 research articles were collected. Based on their title and abstract, these articles were further screened by removing duplicates and non-original articles. The titles and abstracts of the screened articles are directly related to the mean absorbed doses to the heart, LAD, and left-lung during the treatment of the left-sided female breast cancer patients using different RT modalities in combination with both FB and DIBH techniques. This yielded 105 relevant studies. After reading the full text of these studies, 19 of them were identified as suitable studies and considered eligible.

**Figure 2** shows a flow diagram for the meta-analysis Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) of the eligible studies. **Table 3** summarizes the characteristic study details of the 19 eligible studies. In the 19 eligible studies, there were a total of 634 patients. By study design, the 19 included eligible studies are 1 prospective study, 15 retrospective studies, and 3 RCTs with the total sample sizes of 15, 523, and 96, respectively. The sample size of the individual study ranges from 12 to 69. The total of 634 patients treated using different RT modalities combined with both DIBH and FB techniques: 390 patients using 3D-CRT modality only, 69 patients using 3D-CRT plus IMRT modalities, 111 patients using only IMRT modality, 30 patients using VMAT modality only, 20 patients using IMRT plus VMAT modalities, and 14 patients using 3D-CRT, VMAT, & PBT modalities. Total doses

(Gy) per fractions prescribed to the patients in the eligible studies included 37.5/16, 40/16, 40/15, 40.05/15, 42.4/16, 42.5/16, 42.56/16, 45/25, 50/25, 50.4/28, 52.2/30. Six of the 19 studies had a boost, and the remaining 13 studies did not have a boost. From a total of 19 eligible studies, only eighteen of them have reported their study period (2006 -2018). Of the 19 eligible studies, only 15 of them reported the patients' age in the range 25–79.

### Quality assessment and publication bias

We used two different quality assessment tools to evaluate the 19 included eligible studies presented in **Table 3**. Sixteen out of 19 studies were evaluated using NOS from 9 scores by considering standards of studies with scores < 5 as high risk and  $\geq 5$  as low risk.<sup>28</sup> Six of these sixteen studies scored 6 points each, while the remaining ten studies scored 7 points each. All the 16 included studies resulted in low risk based on these scores and are presented in **Table 2**. Cochrane collaboration's risk of bias tool was also applied to evaluate the quality of the remaining 3 RCT studies. The evaluation of these three studies was from the seven scores. Thus, two of them scored six low-risks and one high risk. The third study scored two high-risks and five low-risks and is displayed in **Figure 1**. Publication bias was estimated using the funnel plots shown in **Figures 6 a, b, and c** for heart, LAD, and left-lung studies, respectively.

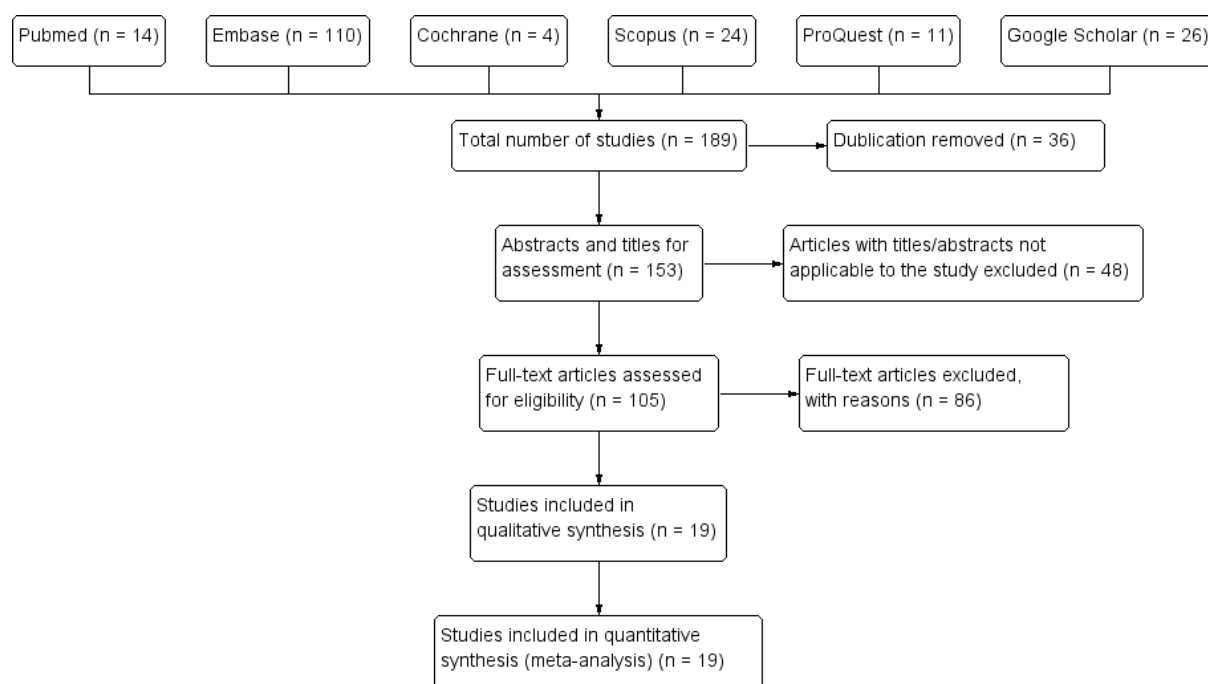


**Figure 2.** Flow diagram for the meta-analysis Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

**Table 3. The nineteen Eligible studies searched with their study characteristics.**

| Author, publication year      | Country        | Design of the study | Period of the study | RT technique used   | Total dose (Gy)/ fractions                         | n-DIBH | n-FB | Total sample (N) | Mean and/or (range) of age by year | DIBH technique  | Treated area                           |
|-------------------------------|----------------|---------------------|---------------------|---------------------|----------------------------------------------------|--------|------|------------------|------------------------------------|-----------------|----------------------------------------|
| Aiello <sup>29</sup> 2019     | Italy          | Retrospective       | 2018                | 3D-CRT              | 50/25 & 40.05/15 with 10/5, 9/3, & 12/4 boost      | 40     | 40   | 40               | 53 (36-76)                         | vDIBH (RPM)     | Breast + boost                         |
| Al-Hammadi <sup>30</sup> 2018 | Qatar          | Retrospective       | 2015 – 2017         | IMRT                | 50/25 with 16/8 electron boost                     | 52     | 54   | 54               | 30-64                              | vDIBH (RPM)     | Breast/CW ± SCV LN + boost             |
| Bartlett <sup>31</sup> 2015   | United Kingdom | RCT                 | 2013 – 2014         | 3D-CRT              | 40/15                                              | 28     | 28   | 28               | 25–79                              | vDIBH (AlignRT) | Breast/CW                              |
| Cao <sup>21</sup> 2019        | USA            | Retrospective       | 2014 – 2017         | IMRT                | 50/25 & 50.4/28                                    | 57     | 57   | 57               | 32–78                              | vDIBH (RPM)     | Breast + CW                            |
| Jagsi <sup>32</sup> 2018      | USA            | RCT                 | 2006 – 2012         | IMRT & 3D-CRT       | 50.4/ 28 with 10/2 boost & 52.2/30 with 10/2 boost | 28     | 26   | 54               | 50.43                              | ABC             | Breast/CW + SCV + ICV + IMC LN + boost |
| Joo <sup>33</sup> 2015        | South Korea    | Retrospective       | 2012 – 2015         | 3D-CRT              | 50/25 with 10/2 boost                              | 30     | 30   | 30               | 48 (25–77)                         | vDIBH (RPM)     | Breast/CW ± SCV + Ax                   |
| Kathpai <sup>34</sup> 2016    | USA            | Retrospective       | 2012 – 2013         | 3D-CRT              | 50/25                                              | 12     | 12   | 12               | 42-70                              | vDIBH (AlignRT) | Breast/CW                              |
| Kim <sup>35</sup> 2018        | USA            | Retrospective       | 2015 – 2016         | 3D-CRT              | 42.56/16, 50/25, 50.4/28, & 45/25                  | 69     | 69   | 69               | 54.1                               | vDIBH (other)   | Breast/CW                              |
| Lawler <sup>3</sup> 2017      | Ireland        | Retrospective       | 2008 – 2013         | 3D-CRT              | 40.05-50/15-25                                     | 28     | 28   | 28               | 57.39 (37-75)                      | RPM             | Breast/CW ± SCV                        |
| Mathieu <sup>36</sup> 2020    | Canada         | Retrospective       | 2012 – 2016         | 3D-CRT              | 42.5/16                                            | 23     | 23   | 23               | 54 (37-73)                         | vDIBH (other)   | Breast/CW + Ax                         |
| Nguyen <sup>37</sup> 2018     | USA            | Retrospective       | 2012 – 2015         | 3D-CRT              | 50.4/28-50/25                                      | 49     | 49   | 49               | 26.5–69.9                          | vDIBH (other)   | Breast/CW ± SCV + IMC LN               |
| Oechsner <sup>38</sup> 2019   | Germany        | Retrospective       | 2013 – 2015         | 3D-CRT              | 50/25                                              | 31     | 31   | 31               | NA                                 | vDIBH (RPM)     | Breast/CW                              |
| Ranger <sup>39</sup> 2018     | United Kingdom | RCT                 | NA                  | 3D-CRT, VMAT, & PBT | 40/15                                              | 14     | 14   | 14               | 31-68                              | vDIBH (other)   | Breast/CW ± IMC LN                     |
| Rochet <sup>40</sup> 2015     | USA            | Retrospective       | 2011 – 2012         | 3D-CRT              | 50/25, 50.4/28, & 42.4/16 with 10/2 boost          | 35     | 35   | 35               | 35-69                              | vDIBH (other)   | Breast/CW ± SCV + Ax + IMC LN + boost  |
| Sakka <sup>41</sup> 2017      | Germany        | Retrospective       | 2015                | IMRT, VMAT          | 50.4/28                                            | 20     | 20   | 20               | <70                                | vDIBH (RPM)     | Breast/CW                              |
| Sripathi <sup>42</sup> 2017   | India          | Prospective         | 2014 – 2016         | 3D-CRT & IMRT       | 50/ 25                                             | 15     | 15   | 15               | NA                                 | vDIBH (RPM)     | Breast/CW + SCV                        |
| Tamburella <sup>43</sup> 2017 | Switzerland    | Retrospective       | 2016 – 2018         | VMAT                | 50/25 with 60/25 boost                             | 30     | 30   | 30               | NA                                 | vDIBH (other)   | Breast/CW ± SCV + Ax + IMC LN + boost  |
| Wiant <sup>44</sup> 2015      | USA            | Retrospective       | 2014                | 3D-CRT              | 50.4/28                                            | 25     | 25   | 25               | NA                                 | vDIBH (other)   | Breast                                 |
| Yeung <sup>45</sup> 2015      | Canada         | Retrospective       | 2013                | 3D-CRT              | 40/16, 42.5/16, 45/25, 50/25, & 37.5/16            | 20     | 20   | 20               | 34–69                              | vDIBH (other)   | Breast/CW ± SCV + Ax + IMC LN          |

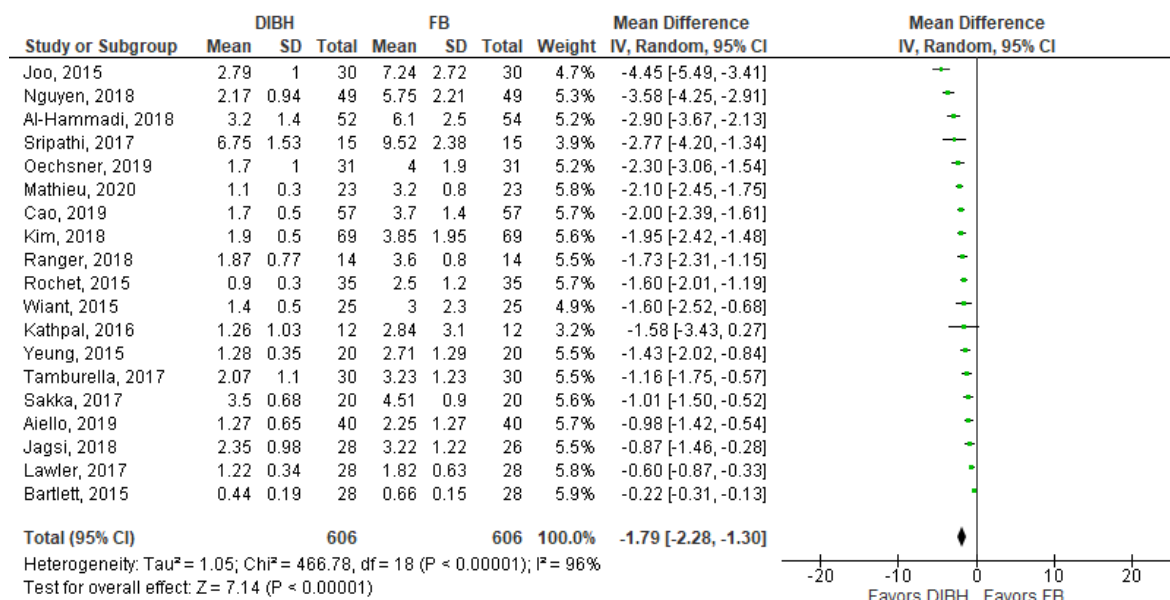


**Figure 3. Forest plot of heart analysis using the weighted mean difference in Gy: 95% Confidence interval (95% CI), Standard deviation (SD), Free-breathing (FB), Deep inspiration breath-hold (DIBH), Interval variable (IV), Random-effects meta-analysis model (Random), Mean dose (Mean) in Gy, Relative contribution (Weight).**

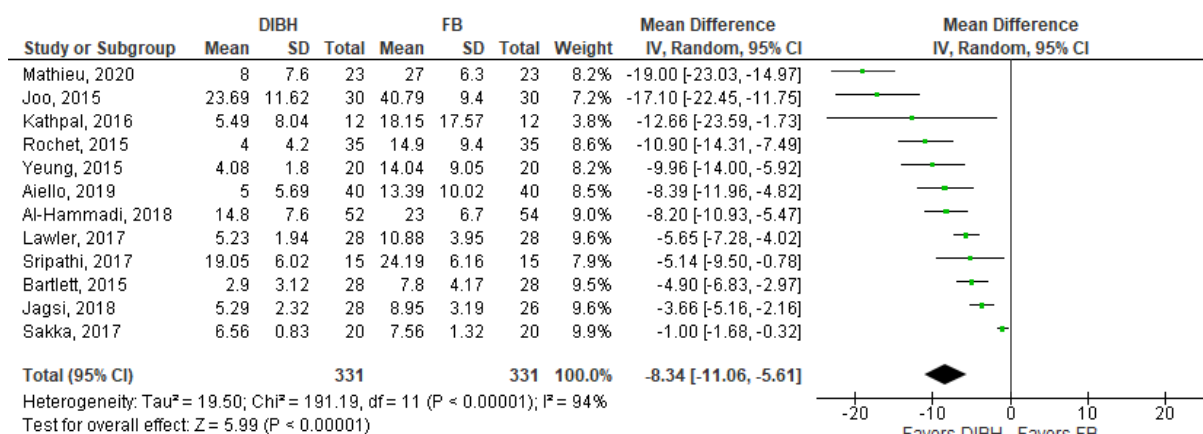


**Figure 4. Forest plot of left anterior descending (LAD) coronary artery analysis using the weighted mean difference in Gy: 95% Confidence interval (95% CI), Standard deviation (SD), Free-breathing (FB), Deep inspiration breath-hold (DIBH), Interval variable (IV), Random-effects meta-analysis model (Random), Mean dose (Mean) in Gy, Relative contribution (Weight).**

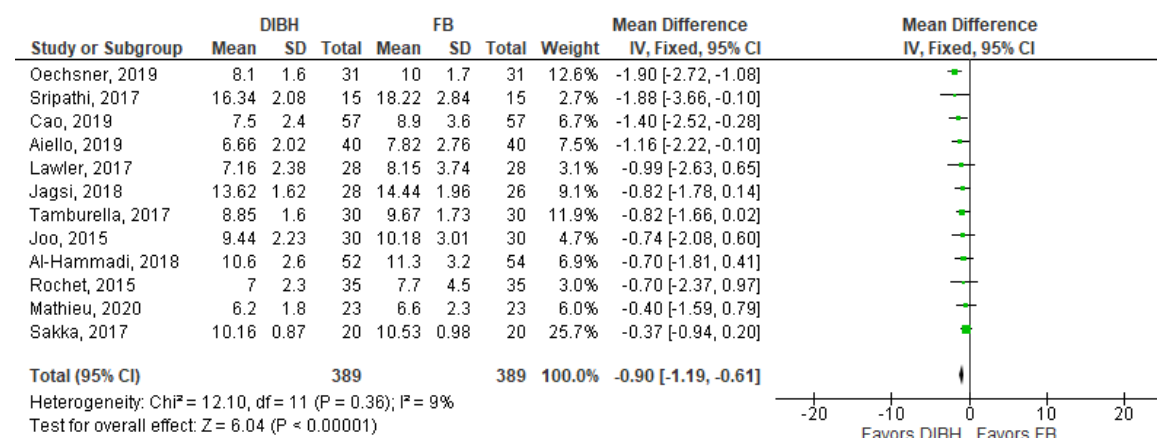


**Figure 5. Forest plot of lung analysis using the weighted mean difference in Gy: 95% Confidence interval (95% CI), Standard deviation (SD), Free-breathing (FB), Deep inspiration breath-hold (DIBH), Interval variable (IV), Fixed-effects meta-analysis model (Random), Mean dose (Mean) in Gy, Relative contribution (Weight).**

## Outcomes of meta-analysis

### Heart

Mean absorbed doses to the heart were reported comprehensively by the nineteen included studies from 606 left-sided breast cancer patients under different RT modalities combined with DIBH and 606 left-sided breast cancer patients under different RT modalities combined with FB. The heterogeneity between the studies was evaluated and was found significant ( $\chi^2 = 466.78$ ,  $P = 0.00001$ ,  $I^2 = 96\%$ ), therefore the pooled effect was determined using a random-effects meta-analysis model. The results of the overall pooled effect proved that the change between the mean heart doses during different RT with DIBH and FB of the left-sided breast cancer patients was statistically significant (weighted MD = -1.79 Gy; 95% CI (-2.28, -1.30);  $P = 0.00001$ ; **Figure 3**). The mean absorbed heart dose in the 19 eligible studies was advantageous and in favor of dose reduction with the DIBH than FB techniques. The symmetry of the funnel plot of the included studies about mean heart dose was displayed in **Figure 6a**.

### LAD

Mean absorbed doses to the LAD were reported comprehensively by the twelve included studies from 331 left-sided breast cancer patients under different RT modalities combined with DIBH and 331 left-sided breast cancer patients under different RT modalities combined with FB. The heterogeneity between the studies was evaluated and was found significant ( $\chi^2 = 191.19$ ,  $P = 0.00001$ ,  $I^2 = 94\%$ ), therefore the pooled effect was determined using a random-effects meta-analysis model. The results of the overall pooled effect proved that the change between the mean LAD doses during different RT with DIBH and FB of the left-sided breast cancer patients was statistically significant (weighted MD = -8.34 Gy; 95% CI (-11.06, -5.61);  $P = 0.00001$ ; **Figure 4**). The mean absorbed LAD dose in the 12 eligible studies was advantageous and in favor of dose reduction with the DIBH than FB techniques. The symmetry of the funnel plot of the included studies about mean LAD dose was displayed in **Figure 6b**.

### Left-lung

Mean absorbed doses to the left-lung were reported comprehensively by the twelve included studies from 389 left-sided breast cancer patients under different RT modalities combined with DIBH and 389 left-sided breast cancer patients under different RT modalities combined with FB. The heterogeneity between the studies was evaluated and was found insignificant ( $\chi^2 = 12.10$ ,  $P = 0.36$ ,  $I^2 = 9\%$ ); therefore, the pooled effect was determined using a fixed-effects meta-analysis model. The results of the overall pooled effect proved that the change between the mean left-lung doses during different RT with DIBH and FB of the left-sided breast cancer patients was statistically significant (weighted MD = -0.90 Gy; 95% CI (-1.19, -0.61);  $P = 0.00001$ ; **Figure 5**). The mean

absorbed left-lung dose in the 12 included eligible studies were advantageous and in favor of dose reduction with the DIBH than FB techniques. The symmetry of the funnel plot of the included studies about the mean left-lung dose was displayed in **Figure 6c**.

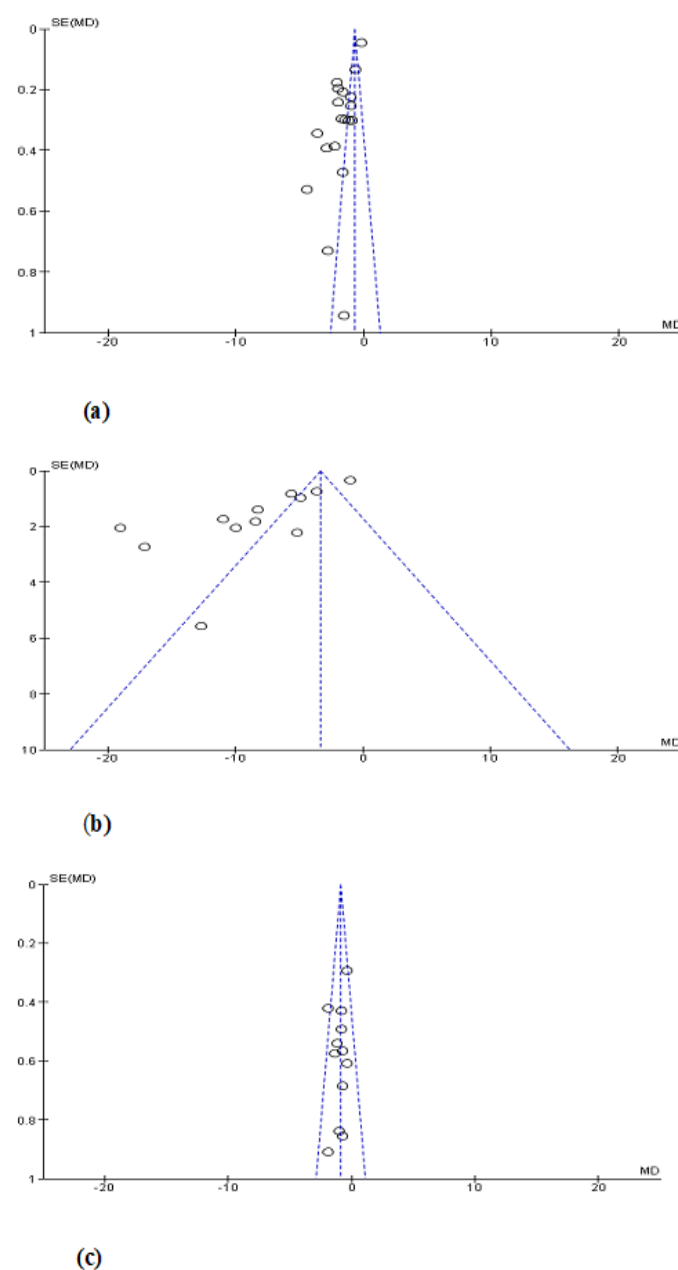


**Figure 6.** (a) Funnel plot for the heart. (b) Funnel plot for left anterior descending (LAD) coronary artery. (c) Funnel plot for lung. The standard error (SD), Weighted mean difference (MD) in Gy

## Discussion

Most patients can tolerate left breast cancer RT using DIBH technique. However, patients should be screened and carefully selected based on factors such as the ability to tolerate the technique, cost, and patient convenience. The sparing of the heart, LAD, and left-lung during the combined use of different RT modalities with DIBH and FB techniques to treat left-sided breast cancer patients varies from one RT modality to another RT modality. For example, Mast et al. found a significant additional mean absorbed dose decrement in the heart, LAD, and left-lung using IMRT compared to 3D-CRT in both DIBH and FB combinations for the total prescribed dose of 42.56 Gy in 16 fractions.<sup>46</sup> Osman, Hol, Poortmans, & Essers also found the mean absorbed doses to the heart and left-lung decreased in VMAT compared to 3D-CRT in both techniques combinations for the total prescribed dose of 42.56 Gy in 16 fractions.<sup>47</sup> In another study done by Pham et al., VMAT showed a better sparing of the heart, LAD, and left-lung in both DIBH and FB combinations than IMRT for the total prescribed dose of 50 Gy in 25 fractions.<sup>48</sup> For the prescribed dose of 40 Gy in 15 fractions, Ranger et al. found that the mean absorbed doses to the heart using proton beam therapy (PBT) were less than from the VMAT combined with DIBH and FB systems.<sup>39</sup> Sakka, Kunzelmann, Metzger, and Grabenbauer also found a significant decrement in the mean absorbed heart and LAD doses using IMRT than VMAT in combination with DIBH and FB techniques. However, the absorbed mean left-lung dose showed an increment in IMRT compared to VMAT for the total prescribed dose of 50.4 Gy in 28 fractions.<sup>49</sup> The combinations of modern RT modalities with DIBH can better spare OARs compared to 3D-CRT combinations with DIBH. Because solely using contemporary RT modalities such as IMRT, VMAT, and PDT for breast cancer treatment can reduce dose to the OARs and further dose reduction, these modern RT modalities should be applied in conjunction with DIBH techniques. However, the dose reductions to the OARs during breast RT combined with DIBH techniques were not analyzed statistically before this study. A better understanding of the pooled OARs dose reduction during the treatment of left-sided breast cancer patients using different RT modalities in combination with DIBH techniques compared to FB technique combination has a crucial role in decreasing the probability of long-term complications. This study provides comprehensive and determined helpful information regarding dose reductions to the heart, LAD, and left-lung during the treatment of left-sided breast cancer patients using different RT modalities in combination with DIBH techniques compared to FB technique.

Regarding the mean absorbed heart dose, all the 19 eligible studies were advantageous and favored dose reduction using different RT modalities combined with the DIBH techniques. However, a study by Joo et al. was the most effective relatively with the maximum weighted MD dose = -4.45 Gy and its 95%

CI (-5.49, -3.41), and a study that was done by Bartlett et al. was the least effective with the minimum weighted MD dose = -0.22 Gy and 95% CI (-0.31, -0.13).<sup>31,33</sup> However, the compared overall pooled effects of DIBH combined RT modalities and FB RT modalities applied on the heart proved that the mean absorbed heart doses showed a pronounced change and were statistically significant (weighted MD = -1.79 Gy; 95% CI (-2.28, -1.30);  $P = 0.00001$ ). Regarding the mean absorbed LAD dose, all the 12 eligible studies were advantageous and favored dose reduction using DIBH combinations with different RT modalities. However, a study by Mathieu et al. was the most effective relatively with the maximum weighted MD dose = -19 Gy, and 95% CI (-23.03, -14.97), and a study that was done by Sakka et al. was the least effective with the minimum weighted MD dose = -1.0 Gy and 95% CI (-1.68, -0.32).<sup>36,41</sup> But, the compared overall pooled effects of DIBH combined RT modalities and FB RT modalities applied on the LAD proved that the mean absorbed LAD doses showed a pronounced change and were statistically significant (weighted MD = -8.34 Gy; 95% CI (-11.06, -5.61);  $P = 0.00001$ ). Regarding the mean absorbed left-lung dose, all the 12 eligible studies were advantageous and favored dose reduction using DIBH combinations with different RT modalities. However, a study by Oechsner et al. was the most effective relatively with the maximum weighted MD dose = -1.9 Gy, and 95% CI (-2.72, -1.08), and a study by Sakka et al. was the least effective with the minimum weighted MD dose = -0.37 Gy and 95% CI (-0.94, 0.20).<sup>38,41</sup> But, the compared overall pooled effects of DIBH combined RT modalities and FB RT modalities applied on the left-lung proved that the mean absorbed left-lung doses showed a pronounced change and were statistically significant (weighted MD = -0.90 Gy; 95% CI (-1.19, -0.61);  $P = 0.00001$ ).

The combined use of different RT modalities with DIBH techniques during the treatment of left-sided breast cancer patients showed a sound decrement in the mean absorbed doses of the heart, LAD, and left-lung compared to FB combination. Thus, this demonstrates that different contemporary RT modalities and 3D-CRT in conjunction with DIBH techniques can spare the mentioned three OARs better. Based on the total pooled effect of weighted MD doses of the heart, LAD, and left-lung, the mean absorbed doses using DIBH showed decrement by 1.79, 8.34, and 0.90 Gy. So, the combined use of different RT modalities with DIBH techniques would be preferable to FB combination during the treatment of left-sided breast cancer patients to minimize the OARs long-term complications.

The presence of different types of biases could result in many limitations of this meta-analysis. The first limitation could result in because the included studies were from different study designs such as a prospective study, 15 retrospective studies, and 3 RCTs. The second limitation of this study could be from a small number of left-sided breast cancer patients analyzed in the study. The third limitation could also result in because the

outcome assessors were not blinded in all included studies, 2 of the 3 randomized studies have incomplete outcome data, and all the other non-randomized studies have not scored for NOS VII, there were dropouts or attrition biases because of the patients' intolerance, and inconvenience of using DIBH in studies such as Al-Hammadi 2018, Bartlett 2015, Cao 2019, Jagsi 2018, Joo 2015, Kathpal 2016, Mathieu 2020, Sakka 2017, and Kim 2018.

This study demonstrated that different RT modalities in conjunction with DIBH techniques used to treat left-sided breast cancer patients have a significant role in dose reduction to the heart, LAD, and left-lung. So, by using a larger sample size, studies from similar study designs, and bias could have been minimized, reducing the study's limitation.

## Conclusion

This meta-analysis demonstrated that different RT modalities combined with DIBH techniques in treating breast cancer possibly reduce doses to the heart, LAD, and left-lung better than FB combination. Therefore, the treatment of left-sided breast cancer patients using different RT modalities combined with DIBH techniques should be a better option to combat long-term radiation dose effects on the mentioned three OARs.

## References

1. 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: A Cancer Journal for Clinicians*. 2018;68(6):394-424. <https://doi.org/10.3322/caac.21492>
2. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *International Journal of Cancer*. 2018;144(8):1941-1953. <https://doi.org/10.1002/ijc.31937>
3. Lawler G and Leech M. Dose sparing potential of deep inspiration breath-hold technique for left breast cancer radiotherapy organs-at-risk. *Anticancer Research*. 2017;37:883-90. <https://doi.org/10.21873/anticancer.11394>
4. Brownlee Z, Garg R, Listo M, Zavitsanos P, Wazer DE, Huber KE. Late complications of radiation therapy for breast cancer: evolution in techniques and risk over time. *Gland Surg*. 2018;7:371-8. <https://doi.org/10.21037/gs.2018.01.05>
5. Macrie BD, Donnelly ED, Hayes JP, et al. A cost-effective technique for cardiac sparing with deep inspiration-breath hold (DIBH). *Physica Medica*. 2015;31:733-7. <https://doi.org/10.1016/j.ejmp.2015.06.006>
6. Chi HC, Tsai CY, Tsai MM, Yeh CT, Lin KH. Roles of Long Noncoding RNAs in Recurrence and Metastasis of Radiotherapy-Resistant Cancer Stem Cells. *International Journal of Molecular Sciences*. 2017;18(9). <https://doi.org/10.3390/ijms18091903>
7. Lomax ME, Folkes LK, O'Neill P. Biological consequences of radiation-induced DNA damage: relevance to radiotherapy. *Clinical Oncology*. 2013;25:578-85. <https://doi.org/10.1016/j.clon.2013.06.007>
8. Zhu Q, Kirova YM, Cao L, Arsene-Henry A, Chen J. Cardiotoxicity associated with radiotherapy in breast cancer: A question-based review with current literatures. *Cancer Treatment Reviews*. 2018;68:9-15. <https://doi.org/10.1016/j.ctrv.2018.03.008>
9. Taylor CW, Kirby AM. Cardiac Side-effects From Breast Cancer Radiotherapy. *Clinical Oncology*. 2015;27:621-9. <https://doi.org/10.1016/j.clon.2015.06.007>
10. Poitevin-Chacón MA, Ramos-Prudencio R, Rumoroso-García JA, Rodríguez-Laguna A, Martínez-Robledo JC. Voluntary breath-hold reduces dose to organs at risk in radiotherapy of left-sided breast cancer. *Reports of Practical Oncology and Radiotherapy*. 2020;25:104-8. <https://doi.org/https://doi.org/10.1016/j.rpor.2019.12.016>
11. Hepp R, Ammerpohl M, Morgenstern C, et al. Deep inspiration breath-hold (DIBH) radiotherapy in left-sided breast cancer: Dosimetrical comparison and clinical feasibility in 20 patients. *Strahlentherapie und Onkologie*. 2015;191:710-6. <https://doi.org/10.1007/s00066-015-0838-y>
12. Grantzau T, Thomsen MS, Væth M, Overgaard J. Risk of second primary lung cancer in women after radiotherapy for breast cancer. *Radiotherapy and Oncology*. 2014;111:366-73. <https://doi.org/10.1016/j.radonc.2014.05.004>
13. van den Bogaard VA, Ta BD, van der Schaaf A, 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. *Journal of Clinical Oncology*. 2017;35:1171-8. <https://doi.org/10.1200/jco.2016.69.8480>
14. Prunaretty J, Boisselier P, Aillères N, et al. Tracking, gating, free-breathing, which technique to use for lung stereotactic treatments? A dosimetric comparison. *Reports of Practical Oncology and Radiotherapy*. 2019;24:97-104. <https://doi.org/10.1016/j.rpor.2018.11.003>
15. Yu PC, Wu CJ, Tsai YL, et al. Dosimetric analysis of tangent-based volumetric modulated arc therapy with deep inspiration breath-hold technique for left breast cancer patients. *Radiation Oncology*. 2018;13:231. <https://doi.org/10.1186/s13014-018-1170-3>

16. Boda-Heggemann J, Knopf A-C, Simeonova A, et al. DIBH (Deep Inspiratory Breath Hold)-based radiotherapy – a clinical review. *International Journal of Radiation Oncology Biology Physics*. 2015;94. <https://doi.org/10.1016/j.ijrobp.2015.11.049>
17. Karpf D, Sakka M, Metzger M and Grabenbauer GG. Left breast irradiation with tangential intensity modulated radiotherapy (t-IMRT) versus tangential volumetric modulated arc therapy (t-VMAT): trade-offs between secondary cancer induction risk and optimal target coverage. *Radiation Oncology*. 2019;14:156. <https://doi.org/10.1186/s13014-019-1363-4>
18. 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. <https://doi.org/10.3389/fonc.2018.00087>
19. Wong JW, Sharpe MB, Jaffray DA, et al. The use of active breathing control (ABC) to reduce margin for breathing motion. *International Journal of Radiation Oncology Biology Physics*. 1999;44:911-9. [https://doi.org/10.1016/s0360-3016\(99\)00056-5](https://doi.org/10.1016/s0360-3016(99)00056-5)
20. Latty D, Stuart KE, Wang W, Ahern V. Review of deep inspiration breath-hold techniques for the treatment of breast cancer. *Journal of Medical Radiation Sciences*. 2015;62:74-81. <https://doi.org/10.1002/jmrs.96>
21. Cao N, Kalet AM, Young LA, et al. Predictors of cardiac and lung dose sparing in DIBH for left breast treatment. *Physica Medica*. 2019;67:27-33. <https://doi.org/10.1016/j.ejmp.2019.09.240>
22. Nissen HD, Appelt AL. Improved heart, lung and target dose with deep inspiration breath hold in a large clinical series of breast cancer patients. *Radiotherapy and Oncology*. 2013;106:28-32. <https://doi.org/10.1016/j.radonc.2012.10.016>
23. Bartlett FR, Colgan RM, Carr K, et al. The UK HeartSpare Study: Randomised evaluation of voluntary deep-inspiratory breath-hold in women undergoing breast radiotherapy. *Radiotherapy and Oncology*. 2013;108:242-7. <https://doi.org/10.1016/j.radonc.2013.04.021>
24. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine*. 2009;6:e1000097. <https://doi.org/10.1371/journal.pmed.1000097>
25. Takeshima N, Sozu T, Tajika A, Ogawa Y, Hayasaka Y, Furukawa TA. Which is more generalizable, powerful and interpretable in meta-analyses, mean difference or standardized mean difference? *BMC Medical Research Methodology*. 2014;14:30. <https://doi.org/10.1186/1471-2288-14-30>
26. Faraone SV. Interpreting estimates of treatment effects: implications for managed care. *Pharmacy and Therapeutics*. 2008;33:700-11.
27. Sterne J, Harbord R. Funnel Plots in Meta-analysis. *Stata Journal*. 2004;4:127-41. <https://doi.org/10.1177/1536867X0400400204>
28. Veronese N, Cereda E, Solmi M, et al. Inverse relationship between body mass index and mortality in older nursing home residents: a meta-analysis of 19,538 elderly subjects. *Obesity Reviews*. 2015;16:1001-15. <https://doi.org/10.1111/obr.12309>
29. Aiello D, Borzi GR, Marino L, Umina V, Di Grazia AM. Comparison of deep inspiration breath hold and free breathing technique in left breast cancer irradiation: a dosimetric evaluation in 40 patients. *Journal of Radiation Oncology*. 2019;8:89-96. <https://doi.org/10.1007/s13566-019-00381-3>
30. Al-Hammadi N, Caparrotti P, Naim C, et al. Voluntary deep inspiration breath-hold reduces the heart dose without compromising the target volume coverage during radiotherapy for left-sided breast cancer. *Radiology and Oncology*. 2018;52:112-20. <https://doi.org/10.1515/raon-2018-0008>
31. Bartlett FR, Colgan RM, Donovan EM, et al. The UK HeartSpare Study (Stage IB): Randomised comparison of a voluntary breath-hold technique and prone radiotherapy after breast conserving surgery. *Radiotherapy and Oncology*. 2015;114:66-72. <https://doi.org/10.1016/j.radonc.2014.11.018>
32. Jaggi R, Griffith KA, Moran JM, et al. A Randomized Comparison of Radiation Therapy Techniques in the Management of Node-Positive Breast Cancer: Primary Outcomes Analysis. *International Journal of Radiation Oncology Biology Physics*. 2018;101:1149-58. <https://doi.org/10.1016/j.ijrobp.2018.04.075>
33. Joo JH, Kim SS, Ahn SD, et al. Cardiac dose reduction during tangential breast irradiation using deep inspiration breath hold: A dose comparison study based on deformable image registration. *Radiation Oncology*. 2015;10. <https://doi.org/10.1186/s13014-015-0573-7>
34. Kathpal M, Tinnel B, Sun K, et al. Deep inspiration breath hold with electromagnetic confirmation of chest wall position for adjuvant therapy of left-sided breast cancer: Technique and accuracy. *Practical Radiation Oncology*. 2016;6:e195-e202. <https://doi.org/10.1016/j.prro.2015.12.008>
35. Kim A, Kalet AM, Cao N, et al. Effects of Preparatory Coaching and Home Practice for Deep Inspiration Breath Hold on Cardiac Dose for Left Breast Radiation Therapy. *Clinical Oncology*. 2018; 30: 571-7. <https://doi.org/10.1016/j.clon.2018.04.009>
36. Mathieu D, Bedwani S, Mascolo-Fortin J, et al. Cardiac Sparing with Personalized Treatment Planning for Early-stage Left Breast Cancer. *Cureus*. 2020;12:e7247. <https://doi.org/10.7759/cureus.7247>
37. Nguyen MH, Lavilla M, Kim JN, Fang LC. Cardiac sparing characteristics of internal mammary chain radiotherapy using deep inspiration breath hold for left-sided breast cancer. *Radiation Oncology*. 2018;13. <https://doi.org/10.1186/s13014-018-1052-8>
38. Oechsner M, Düsberg M, Borm KJ, Combs SE, Wilkens JJ and Duma MN. Deep inspiration breath-hold for left-sided breast irradiation: Analysis of dose-mass histograms and the impact of lung expansion. *Radiation Oncology*. 2019;14. <https://doi.org/10.1186/s13014-019-1293-1>

39. Ranger A, Dunlop A, Hutchinson K, et al. A Dosimetric Comparison of Breast Radiotherapy Techniques to Treat Locoregional Lymph Nodes Including the Internal Mammary Chain. *Clinical Oncology*. 2018;30:346-53. <https://doi.org/10.1016/j.clon.2018.01.017>
40. Rochet N, Drake JI, Harrington K, 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. *Practical Radiation Oncology*. 2015;5:e127-e34. <https://doi.org/10.1016/j.prro.2014.08.003>
41. 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*. 2017;193:800-11. <https://doi.org/10.1007/s00066-017-1167-0>
42. Sripathi L, Ahlawat P, Simson D, et al. Cardiac dose reduction with deep-inspiratory breath hold technique of radiotherapy for left-sided breast cancer. *Journal of Medical Physics*. 2017;42:123-7. [https://doi.org/10.4103/jmp.JMP\\_139\\_16](https://doi.org/10.4103/jmp.JMP_139_16)
43. Tamburella C, Guibert G, Cruz OS, Weber P, Tsousou P. A volumetric Modulated Arc Therapy (VMAT) combined with deep inspiration breath hold (DIBH) technique for adjuvant irradiation for left sided breast cancer. *arXiv preprint arXiv:1706.06867*. 2017.
44. Wiant D, Wentworth S, Liu H, Sintay B. How important is a reproducible breath hold for deep inspiration breath hold breast radiation therapy? *International Journal of Radiation Oncology Biology Physics*. 2015;93:901-7. <https://doi.org/10.1016/j.ijrobp.2015.06.010>
45. Yeung R, Conroy L, Long K, et al. Cardiac dose reduction with deep inspiration breath hold for left-sided breast cancer radiotherapy patients with and without regional nodal irradiation. *Radiation Oncology*. 2015;10:200. <https://doi.org/10.1186/s13014-015-0511-8>
46. Mast ME, van Kempen-Harteveld L, Heijenbrok MW, et al. Left-sided breast cancer radiotherapy with and without breath-hold: does IMRT reduce the cardiac dose even further? *Radiotherapy and Oncology*. 2013;108:248-53. <https://doi.org/10.1016/j.radonc.2013.07.017>
47. Osman SOS, Hol S, Poortmans PM, Essers M. Volumetric modulated arc therapy and breath-hold in image-guided locoregional left-sided breast irradiation. *Radiotherapy and Oncology*. 2014;112:17-22. <https://doi.org/10.1016/j.radonc.2014.04.004>
48. Pham TT, Ward R, Latty D, 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? *Journal of Medical Imaging and Radiation Oncology*. 2016;60:545-53. <https://doi.org/10.1111/1754-9485.12459>
49. Sakka M, Kunzelmann L, Metzger M, Grabenbauer GG. Cardiac dose-sparing effects of deep-inspiration breath-hold in left breast irradiation. *Strahlentherapie und Onkologie*. 2017;193:800-11.