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Clinical benefits of deep inspiration breath-hold in postoperative radiotherapy for right-sided breast cancer: a meta-analysis

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Abstract

Objectives The study aims to emphasize the clinical importance of the Deep Inspiration Breath Hold (DIBH) technique by quantifying its dosimetric advantages over Free Breathing (FB) in reducing radiation exposure to the heart, liver, and lungs for right-sided breast cancer patients. This evidence supports its potential for routine clinical use to mitigate radiation-induced toxicity.

Methods A systematic retrieval of controlled trials comparing DIBH and FB techniques in postoperative radiotherapy for right-sided breast cancer was conducted utilizing the PubMed, Embase, Cochrane Library, and Web of Science databases. The primary outcomes assessed included the doses of adjacent normal tissues (heart, liver, and lungs). Summary standardized mean differences (SMD) along with 95% confidence intervals (CI) were computed, respectively. StataMP 17 software was selected to perform data analysis.

Results The study encompassed an analysis of 313 patients derived from seven online studies, comprising 168 individuals in the DIBH group and 269 individuals in the FB group. The findings indicated that the DIBH group received significantly lower irradiation doses to the heart, liver, and lungs in comparison to the FB group, with statistical significance (heart dose: SMD = -0.63, 95% CI -0.85 to -0.41, $P < 0.05$; liver dose: SMD = -1.15, 95% CI -1.91 to -0.38, $P < 0.05$; lung dose: SMD = -0.79, 95% CI -1.23 to -0.35, $P < 0.05$).

Conclusion This meta-analysis indicated that the application of DIBH during postoperative radiotherapy for right-sided breast cancer markedly decreases radiation exposure to the heart, liver, and lungs, while maintaining consistent tumor dose coverage.

Clinical trial number Not applicable.

Keywords Breast cancer, Radiotherapy, Deep inspiration breath hold, Meta-analysis

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Introduction

As of 2020, breast cancer has emerged as the most prevalent malignant neoplasm among humans, with an estimated incidence of 2.3 million new cases [1]. The morbidity and mortality of breast cancer are increasing and showed the highest mortality rate in females in 2017 [2, 3]. The primary therapeutic modalities for breast cancer encompass surgical intervention, chemotherapy, radiotherapy, and endocrine therapy [4]. Over the past few decades, due to various medical advancements, radiotherapy has been proven to significantly improve overall survival rates [5, 6]. As survival rates increase, the risks of various diseases caused by radiation cannot be ignored [7, 8]. The EBCTCG IPD meta-analysis confirmed that radiotherapy offers a significant survival advantage at 15 years, even for patients with early breast cancer. However, it is also associated with a slightly higher risk of mortality from non-cancer causes. While the average impact on 15-year outcomes is relatively modest (9.3% vs. 7.5% for contralateral breast cancer, and 15.9% vs. 14.6% for non-breast-cancer mortality), these effects can vary considerably depending on the treatment regimen. Moreover, absolute differences in 15-year mortality could be strongly influenced by factors such as tumor laterality (which can affect the cardiac radiation dose), smoking habits (which increase both vascular and lung cancer risks), other vascular risk factors, and particularly the patient's age [9]. This suggests that breast cancer radiotherapy may raise the risk of subsequent lung cancer [10]. Recently, significant efforts have been adopted to minimize superfluous radiation exposure, notably through the adoption of techniques like DIBH, which increases the distance between the heart and the irradiation field to reduce cardiac dose [11]. Importantly, this advanced technique demonstrates a high level of reproducibility and stability throughout the whole treatment period [12–14]. Although as all known, DIBH has been widely applied in left-sided breast cancer radiotherapy, rare studies have explored its benefits for right-sided breast cancer [15]. Early data suggest that DIBH may also confer cardiopulmonary benefits for patients with right-sided breast cancer in radiotherapy treatment, especially when regional lymph nodes are encompassed by the irradiation field [16]. While the risk of heart radiation exposure is generally lower in right-sided treatments, there are indications that DIBH might also offer liver-sparing advantages [17]. However, these observations are preliminary, and more research is needed to substantiate these potential benefits. However, interests in right-sided breast cancer radiotherapy have been steadily growing in recent years [18]. This research will examine the effectiveness of DIBH compared to FB techniques in treatment, with the goal of providing scientific evidence to optimize treatment strategies for right-sided breast cancer.

Materials and methods

Searching methodology

A systematic online search was conducted within the databases of PubMed, Embase, Cochrane Library, and Web of Science, utilizing a combination of Medical Subject Headings and free-text terms. Searching strategy incorporated the terms 'breast neoplasms,' 'radiotherapy,' and 'deep inspiration breath hold,' along with their respective free-text alternatives, with a deadline set of August 13, 2024). This analysis was confined to articles published in English. Furthermore, we conducted a manual review of the reference checklists of all retrieved essays to identify potentially relevant studies. The data were evaluated independently by two researchers (LZC and SXR), without any discrepancies addressed through discussion.

Inclusion criteria

The guiding principles of PICOS (Participants, Intervention, Comparison, Outcomes, and Study design) were utilized in entire studies that were included in this analysis. The criteria for inclusion were as follows: (1) Participants [P]: The study included patients who were pathologically diagnosed with right-sided breast cancer, confirmed to be without distant metastasis, and received radiotherapy subsequent to breast-conserving surgery; (2) Intervention [I]: The experimental group of patients were treated in the selection of DIBH. The radiotherapy techniques employed included volumetric modulated arc therapy (VMAT), intensity-modulated radiotherapy (IMRT), and three-dimensional conformal radiotherapy (3D-CRT); (3) Comparison [C]: The control group was treated in the selection of FB, which was also adopted the same three treatment techniques. (4) Outcomes [O]: The outcomes focused on dosimetric indicators for the heart, liver, and lungs, including the mean dose (Dmean) and the proportion of organ volumes receiving specific dose levels: heart V_{5Gy}(%), liver V_{20Gy}(%), lung V_{20Gy}(%). (5) The study design encompasses randomized controlled trials as well as observational studies, which include both cohort and case-control methodologies.

Exclusion criteria

Essays were excluded from consideration based on the following criteria: (1) Review articles, case studies, correspondence, and abstracts; (2) Reports exhibiting inadequate research quality or a significant risk of bias; (3) Essays that did not provide suitable data for aggregation.

Quality evaluation

The Newcastle-Ottawa Scale (NOS) was utilized to assess the potential for bias in nonrandomized research, encompassing three key dimensions: selection, comparability, and outcomes [19]. The evaluation utilized a scoring

system that was with a maximum total of 9 points, allocated as follows: 4 points for selection criteria, 2 points for comparability, and 3 points for outcomes. Studies that achieved a total score of 6 points or higher were deemed as good quality [20].

Statistical analysis

To compare studies on the similar treatment pairs, a paired meta-analysis was conducted using StataMP 17. Continuous outcomes were assessed using the SMD and 95% CI as effective measures. The SMD was calculated using the formula:

$$SMD = \frac{\overline{X}_1 - \overline{X}_2}{SD_{pooled}}$$

Where $\overline{X}_1$ and $\overline{X}_2$ represent the means of the two groups being compared, and SD_{pooled} is the pooled standard deviation of both groups.

Heterogeneity was evaluated with the Cochrane Q test and the I^2 statistic, which measures the proportion of total variation due to heterogeneity rather than random error. A fixed-effect model was employed in condition of the P for the Q test was greater than 0.10 and the I^2 statistic was below 50%. Conversely, a random-effects model was utilized to analyze exhibiting substantial heterogeneity across the data. $P< 0.05$ was considered statistically significant.

Result

Study selection

Following the deduplication process, preliminary searches were executed across PubMed, Embase, Cochrane Library, and Web of Science, resulting in identification of 1,325 primary studies. Letters, reviews, and conference proceedings were excluded, and a re-evaluation of the remaining 1153 articles was filtered based on titles and abstracts, which narrowed it down to 16 studies. After full-text assessments, nine essays were discarded based on excluded criteria, leaving seven studies for inclusion in this meta-analysis. Figure 1 illustrates the flow diagram of the selection process.

Study characteristics

The meta-analysis encompassed seven studies [21–27], involving a cohort of 313 patients with right-sided breast cancer. All studies included were designated as high-quality retrospective research according to the NOS. Table 1 presents a comprehensive overview information associated with the seven studies that were incorporated into the analysis. When a single study reports multiple data sets, each set must be analyzed independently.

Heart dose

We examined the statistical significance of heart dose (Dmean, V_{5Gy}) between the DIBH group and the FB group ($P<0.05$). Heterogeneity tests indicated without significant heterogeneity ($P>0.10$, $I^2 < 50\%$), so a fixed effect model analysis was conducted. The results demonstrated that the DIBH group significantly reduced heart dose than the FB group, with a statistical significance (SMD = -0.63, 95% CI: -0.85 to -0.41, $P<0.05$). Specifically, V_{5Gy} exhibited an SMD of -0.59 (95% CI: -1.04 to -0.14, $P<0.05$), and Dmean showed an SMD of -0.664 (95% CI: -0.90 to -0.39, $P<0.05$) as were shown in Fig. 2.

Liver dose

We conducted an analysis to assess the statistical significance of liver dose (Dmean, V_{20Gy}) between the DIBH group and the FB group ($P<0.05$). Heterogeneity tests showed significant heterogeneity ($P<0.10$, $I^2 > 50\%$), so a random effects model (REM) analysis was conducted. The analysis revealed that the DIBH group is more valid to reduce liver dose compared to the FB group, with statistical significance as illustrated in Fig. 3. (SMD = -1.15, 95% CI: -1.91 to -0.38, $P<0.05$). Specifically, Dmean had an SMD of -1.27 (95% CI: -2.49 to -0.05, $P<0.05$), and V_{20Gy} had an SMD of -1.01 (95% CI: -1.79 to -0.24, $P<0.05$).

Lung dose

We conducted an analysis to assess the statistical significance of lung dose parameters, specifically V_{20Gy} and the mean dose to the right lung, comparing the DIBH group with the FB group ($P<0.05$). Heterogeneity tests indicated significant heterogeneity ($P<0.10$, $I^2 > 50\%$), so prompting the use of a REM for the analysis. The findings indicated that the DIBH significantly decreases lung dose compared to the FB. The differences were statistically significant with an SMD of -0.97 (95% CI: -1.23 to -0.35, $P<0.05$). Specifically, V_{20Gy} exhibited an SMD of -0.66 (95% CI: -1.50 to 0.18, $P>0.05$), and Dmean of Right lung showed an SMD of -0.86 (95% CI: -1.45 to -0.27, $P<0.05$) as were shown in Fig. 4.

Discussion

This study supports the benefits of DIBH adoption in radiotherapy treatment for patients with right-sided breast cancer, offering clinical evidence to advocate for its wider application. Two direct meta-analyses have demonstrated that, in comparison to FB, DIBH significantly decreases the heart dose, the left anterior descending coronary artery dose, and the left lung dose in patients diagnosed with left-sided breast cancer [28, 29]. Another meta-analysis aims to assess the influence of diverse patient positions (prone vs. supine) and breathing techniques (FB vs. DIBH) on the protection of normal tissues

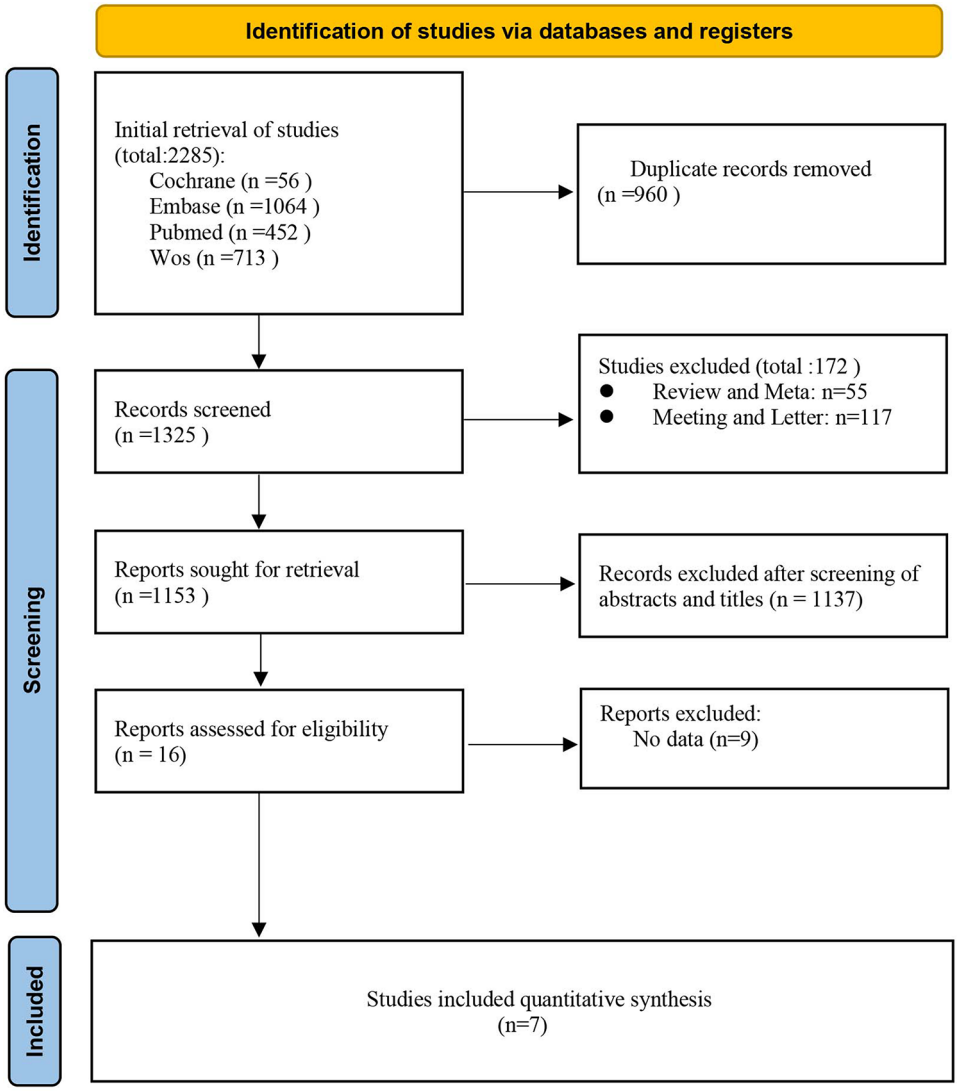

Fig. 1 Flow chart of the search process for the meta-analysis

Table 1 Characteristics of the study included in the meta-analysis. NA not available

Studies	Years	Total patients	Type	RNI	Patients, DIBH/FB	Median age, year	Stage of cancer	Prescription	Techniques	NOS
G.Borgonovo [21]	2022	10	Retrospective	NA	10/10	NA	NA	50 Gy/25 F	IMRT/VMAT	6
N. Aliyeva [22]	2023	70	Retrospective	NA	30/30	NA	IIB-IIIC	50 Gy/25 F	IMRT	6
C. Pandeli [23]	2019	20	Retrospective	NA	10/10	NA	NA	40 Gy/15 F	3D-CRT	6
G. Haji [24]	2019	30	Retrospective	NA	30/30	53	II–III	50 Gy/25 F	3D-CRT	6
C. H. Lin [25]	2019	369	Retrospective	NA	44/144	NA	Tis–II	50 Gy/25 F	IMRT	6
J. Lai [26]	2023	31	Retrospective	NA	31/31	NA	NA	50 Gy/25 F	IMRT	6
M. Essers [27]	2016	14	Retrospective	NA	14/14	NA	NA	42.56 Gy/16 F	3D-CRT	6

Abbreviations Regional Nodal Irradiation (RNI), Newcastle-Ottawa Scale (NOS)

adjacent to tumor area during postoperative radiotherapy for breast cancer, offering valuable insights for clinical practice [30]. This study emphasizes the selection of various radiotherapy techniques rather than the positioning of treatment, and as a result, we are unable to effectively verify the point above.

Radiotherapy has the potential to induce various cardiac complications, which encompass coronary artery disease (CAD), cardiomyopathy, pericardial disease,

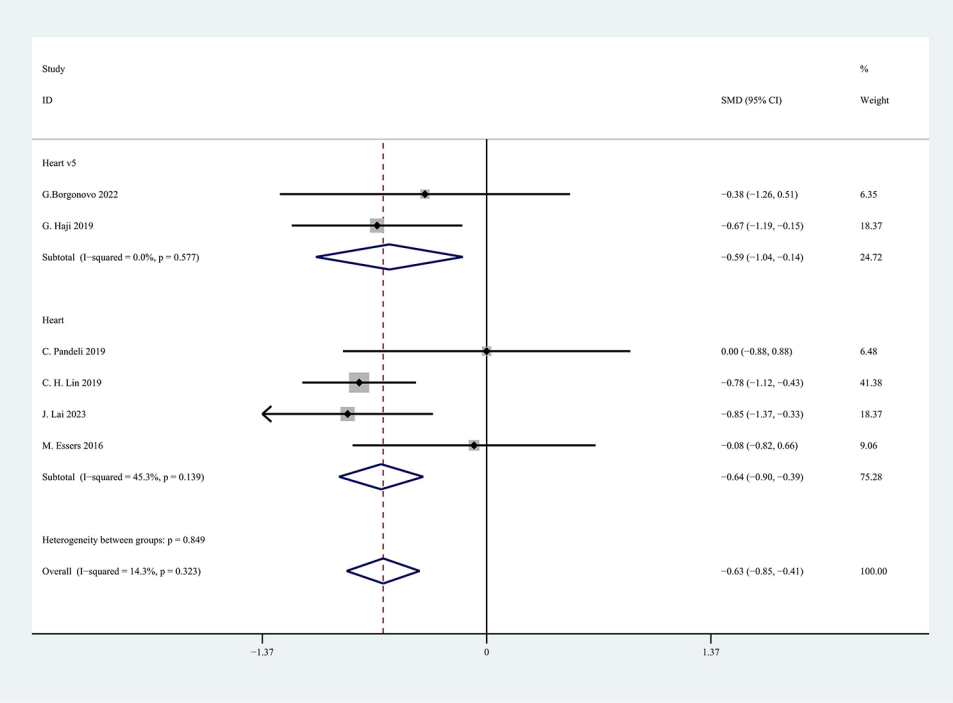

Fig. 2 Forest plot of heart dose between the DIBH group and FB group

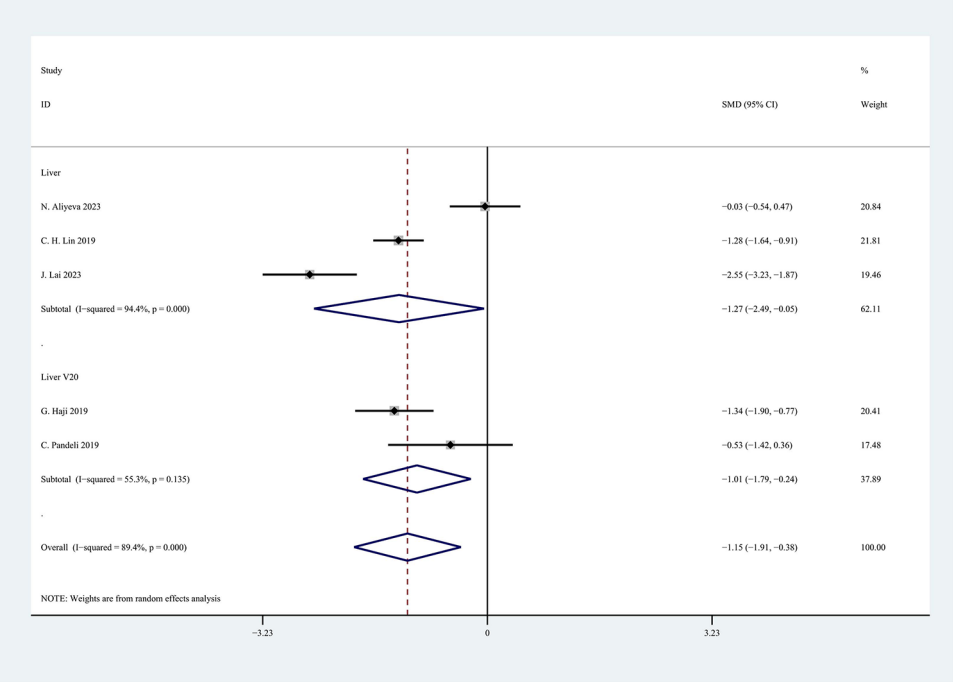

Fig. 3 Forest plot of liver dose between the DIBH group and FB group

valvular heart disease, and arrhythmias [31]. French researchers demonstrated that for every additional 1 Gy to the mean heart dose, the risk of cardiotoxicity increases by approximately 4% (95%CI: 2–6%, P=0.0002) [32]. At present, breast cancer patients often survive for many years after treatment, and the long-term effects of radiotherapy, particularly for heart, become increasingly critical [33]. Unlike short-term side effects, cardiac complications frequently emerge only after many years, underscoring the necessity of protecting the heart during treatment to mitigate these late-onset risks [34]. For instance, radiation may accelerate the progression of

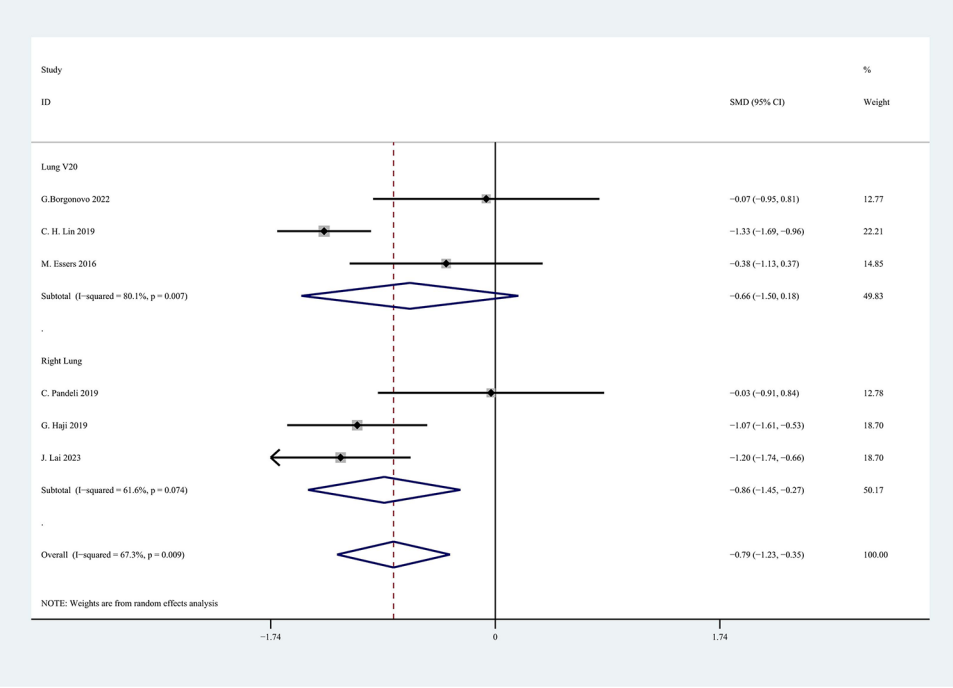

Fig. 4 Forest plot comparing the lung dose between the DIBH group and the FB group

coronary atherosclerosis, increase the risk of myocardial infarction, and can also result in pericarditis, pericardial effusion, as well as fibrosis and calcification of the heart valves. These radiation-induced cardiac complications have been extensively studied and reported in the literature, including the work by Darby et al., which investigates the risk of CAD following breast cancer radiotherapy, and the comprehensive review by Adams et al., which demonstrates the various cardiac diseases associated with radiotherapy [35, 36]. To mitigate the risk of these conditions, it is crucial to minimize the extra irradiation to the heart. This meta-analysis demonstrates that the DIBH group achieved a significant reduction in heart dose (SMD = -0.63, 95% CI -0.85 to -0.41, $P<0.01$). Moreover, all cardiac dose subgroups (Dmean, V_{5Gy}) showed similarly favorable outcomes. These findings indicate that DIBH can effectively reduce cardiac radiation exposure, thereby helping to prevent radiation-induced cardiac complications.

Radiation pneumonitis (RP) represents an acute response to lung injury induced by radiation and constitutes one of the principal dose-limiting toxicities observed in patients receiving chest radiotherapy. The criteria established by the Radiation Therapy Oncology Group indicated that the V_{20Gy} of the lung is commonly correlated with the incidence of RP [37]. In this meta-analysis, the forest plot indicates that, compared to the FB group, DIBH could significantly reduce the right lung dose (SMD = -0.86, 95% CI -1.45 to -0.27); however, this reduction was not observed in V_{20Gy} index. A likely explanation for the aforementioned observation is that during the DIBH procedure, the right lung was inflated to a greater volume. The V_{20Gy} metric was determined based on the dimensions of the irradiation target rather than the volume of the lung itself. On the contrary, mean dose of right lung was determined based on the lung volume. The results indicate that the application of DIBH during postoperative radiotherapy treatment for right-sided breast cancer may reduce the risk of RP.

Extensive studies have explored radiation-induced liver disease over the years. A Study has shown that right-sided radiotherapy can lead to an increase in liver enzymes, indicating subclinical liver injury. For example, in right breast cancer patients, liver function tests such as ALT, AST, and GGT increased by up to 15% post-radiotherapy, even without systemic treatment or pre-existing liver conditions [38]. The liver, especially in abdominal radiotherapy, is a critical organ that must be protected. In right breast radiotherapy, the liver is similarly at risk due to its anatomical proximity, making it a priority in treatment planning to minimize potential radiation damage [39]. The current guidelines for treatment planning in right-sided breast cancer suggest maintaining a mean liver dose (Dmean) within the range of 28–32 Gy to minimize the risk of radiation-induced liver injury [40]. While the liver dose may be significantly lower than the aforementioned recommendations, it is also essential to minimize additional liver exposure for patients with long lifespan. In this meta-analysis, the use of DIBH consistently reduced liver dose across all evaluated subgroups,

such as Dmean and V_{20Gy}. This significant decrease highlights the technique's effectiveness in lowering radiation exposure to the liver, which is essential for minimizing radiation-induced liver toxicity during right-sided breast cancer treatment. The impact of modern chemotherapy, targeted therapy, and immunotherapy on heart and lung disease has significantly altered the landscape of cancer treatment since the era of Darby et al. and the EBCTCG meta-analysis [9, 41, 42]. The findings reinforce the importance of adopting DIBH in clinical practice to enhance liver protection during radiotherapy.

Based on the results above which suggest that DIBH consistently outperforms FB in both left-sided or right-sided breast cancer, leading us to infer that DIBH offers a distinct advantage in breast cancer radiotherapy. However, extensive clinical data are still needed to further substantiate these findings. A significant limitation of this study is the scarcity of research in radiotherapy that specifically addresses right-sided breast cancer, leading to limited number of studies were enrolled. To maintain consistent baseline conditions, we restricted our analysis only to VMAT, IMRT, and 3D-CRT techniques. However, unavoidable heterogeneity among the enrolled studies, such as variations in patient positioning, treatment planning systems, planning algorithms, and prescription selection could be observed. Due to the insufficient studies enrolled, we could not assess the differences between DIBH and FB across different radiotherapy techniques. Additionally, because the contralateral breast and spinal cord typically receive lower radiation doses in right-sided breast cancer radiotherapy, they were not a primary focus of this analysis. Furthermore, acute toxicity was not assessed as a distinct indicator, resulting in the absence of explicit discussion about side effects such as nausea. Another limitation is that we did not include patients with regional nodal irradiation(RNI)and did not taken boost dose calculating in the final dose to heart and lung into account.

Conclusions

This meta-analysis demonstrates that the DIBH technique, when compared to the FB technique in postoperative radiotherapy treatment for right-sided breast cancer, significantly decreased the irradiation exposure to the heart, liver, and lungs. This study indicated that patients with right-sided breast cancer could be benefit from DIBH in mitigating radiation-induced injuries, thereby highlighting its promising prospects for clinical application. Currently, a network meta-analysis is being conducted to further compare the effects of DIBH and FB across different radiotherapy techniques in breast cancer treatment.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-12992-2.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Not applicable.

Author contributions
XR.S and ZC.L: conceptualization, statistical analysis, original draft writing, manuscript review and editing. CX.J and YY.L: data curation. ZY.P and GZ.Y: original draft writing and revising. All authors contributed to the article and approved the submitted version.

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Data availability
The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study, which used de-identified, publicly available data, was exempt from additional institutional review board approval and did not require additional consent.

Competing interests
The authors declare no competing interests.

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