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Deep Inspiration Breath Hold versus Free Breathing in Postoperative Radiotherapy Strategy for Left-sided Breast Cancer with Volumetric Modulated Arc Therapy : A Meta-analysis and Systematic Review

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 09 April 2024 and was last updated on 09 April 2024.

INTRODUCTION

Review question / Objective P: Women patient with left-sided breast cancer who had received operation I: Postoperative radiotherapy with deep inspiration breath hold via Volumetric Modulated Arc Therapy C: Postoperative radiotherapy with free breath via Volumetric Modulated Arc Therapy O: (1) Related outcome of heart dose (2) Related outcome of left anterior descending conronary artery (LAD) dose (3) Related outcome of ipsilateral and contralateral lung dose (4) Related outcome of contralateral breast dose.

Condition being studied Breast cancer is a prevalent malignancy in women, and postoperative radiotherapy (RT) is considered the standard treatment for early-stage cases, which significantly reduces local recurrence and improves long-term survival rates. However, this treatment modality poses risks, as breast tissue irradiation causes substantial radiation exposure to the heart and ipsilateral lung. Notably, left-sided breast cancer (LSBC) irradiation presents an increased risk of cardiac morbidity and mortality due to the proximity of critical anterior cardiac structures, such as the left anterior descending coronary artery (LAD), potentially causing abnormal cardiac perfusion post-irradiation. Darby et al. revealed a correlation between an increased mean heart dose of 1 Gy and indicated a relative risk for major coronary events of 7.4%, highlighting the importance of reducing radiation exposure to mitigate the risk of ischemic heart disease in patients with breast cancer.

Efforts to develop techniques that minimize radiation doses to organs at risk (OAR), particularly the heart and lungs, are ongoing. However, current RT methods still cause incidental cardiac irradiation, requiring the investigation of optimal techniques that reduce heart and ipsilateral lung irradiation while maintaining target coverage.

Deep inspiration breath hold (DIBH) is one of the solutions for LSBC. In this technique, patients are instructed to take a deep breath and hold it during

radiation delivery, causing lung expansion and heart displacement from the chest wall, thereby increasing the distance between the heart and the treatment area. Specialized systems are used to monitor and maintain the breath-hold position throughout treatment, ensuring accuracy. Various devices, such as the real-time position management system or active breathing control , facilitate DIBH, thereby demonstrating favorable feasibility and reproducibility in reducing irradiated heart volume and mean heart dose.

DIBH requires patient cooperation and may extend treatment times due to additional preparation and monitoring steps despite its efficacy. Intensity-modulated RT (IMRT) and volumetric modulated arc therapy (VMAT), in addition to DIBH, provide precise radiation delivery while minimizing OAR exposure. These techniques significantly reduce cardiac and ipsilateral lung doses compared to three-dimensional conformal RT (3D-CRT). VMAT is an advanced form of IMRT that produces highly conformal dose distribution by simultaneously changing dose rate, gantry speed, and MLC position during patient treatment, and VMAT demonstrated efficiency advantages due to shorter delivery times and requiring fewer monitor units.

METHODS

Search strategy A thorough literature review investigating clinical dose, efficacy, and safety for LSBC postoperative RT with DIBH and free breathing (FB) was conducted. The relevant literature was obtained by systematically searching PubMed, EMBASE, and Cochrane Library on March 21, 2024. The literature selection was performed following the search strategy promoted by the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) and the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) guidelines.

Participant or population Female patients with left-sided breast cancer, who had received operation and undergone the subsequent radiotherapy with volumetric modulated arc therapy (VMAT).

Intervention Patients underwent radiotherapy via VMAT with technique of deep inspiration breathing hold technique.

Comparator Patients underwent radiotherapy via VMAT with technique of free breath.

Study designs to be included Published articles in female patients with left-sided breast cancer, who had received operation and undergone the subsequent radiotherapy with volumetric modulated arc therapy (VMAT)patients.

Eligibility criteria The included studies met the following criteria:(1) the study compared the mean heart dose (heart Dmean) of DIBH with FB;(2) the participants were adults and diagnosed with LSBC;(3) the treatment plans were made by VMAT; (4) the study revealed no statistically significant differences in the basic characteristics of the participants;(5) the study included at least one of the following outcomes: heart V5/V25, LAD Dmean/Dmax, ipsilateral lung Dmean/V20, contralateral lung Dmean, and contralateral breast DmeanThe studies were excluded based on the following criteria:(1) failure to meet the inclusion criteria;(2) performed RT for bilateral breast or only right-sided breast;(3) non-English literature;(4) publication types such as conference articles, letters, comments, and reviews.

Information sources A thorough literature review investigating clinical dose, efficacy, and safety for LSBC postoperative RT with DIBH and free breathing (FB) was conducted. The relevant literature was obtained by systematically searching PubMed, EMBASE, and Cochrane Library on March 21, 2024.

Main outcome(s) Related outcome of heart dose : mean dose, heart volume, V5.

Additional outcome(s) (1) Related outcome of heart dose : V10, V20, V25, V30 (2) Related outcome of left anterior descending conronary artery (LAD) dose : mean dose, maximum LAD dose (3) Related outcome of ipsilateral and contralateral lung dose : Mean dose, V5 (4) Related outcome of contralateral breast dose : Mean dose, V5.

Data management Two reviewers (PYC and CHH) independently searched and extracted data from the literature following the inclusion criteria. The extracted information included author, publication year, country, study design, intervention, sample size, follow-up duration, and outcomes. Discrepancies were resolved through discussions among all authors. We used parameters, such as the mean dose (Dmean), the maximum dose (Dmax), and the percentage of the organ volume receiving at least 5 Gy (V5), 20 Gy (V20), and 30 Gy (V30), to analyze dose distributions for the heart, LAD, and left lung. Two reviewers (PYC and PJH) independently verified data extraction, with any disagreements settled by consulting a third reviewer (CCC).

Quality assessment / Risk of bias analysis The Newcastle–Ottawa Scale (NOS) was used to assess the quality of the nonrandomized studies, judged on three broad perspectives: the study group selection, the group comparability, and exposure or outcome of interest ascertainment for case-control or cohort studies, respectively.

Strategy of data synthesis The Cochrane Q and the I2 statistics were used to assess the heterogeneity across studies. P-values of >0.10 and I2< 50% indicate no heterogeneity among the included studies. The random effects model was applied throughout all parameters. Standard mean difference (SMD) and 95% confidence interval (CI) were used to analyze the effects of measurement data. P-values of <0.05 were considered statistically significant. Additionally , we use sensitivity tests to investigate those defined as high heterogeneity.
Moreover, the funnel plot was used to understand the bias of literature publication. The possibility of publication bias is low if the points in the funnel plot are symmetrically distributed on both sides around the middle dashed line and concentrate in the middle. Otherwise, the possibility of publication bias may be high. The Cochrane RevMan version 5.4 software was used for all statistical analyses.

Subgroup analysis We performed a subgroup analysis for tumor bed boost dose, the arc angle of radiotherapy, and radiotherapy with involvement of regional lymph node.

Sensitivity analysis To evaluate whether this a priori definition was significant at other cutoffs, sensitivity analysis was performed to evaluate whether altering the protocal of radiotherapy affected the association with exposured dose.

Language restriction There is no language restriction in this study.

Country(ies) involved Taiwan.

Other relevant information Nil.

Keywords Radiotherapy, volumetric Modulated Arc Therapy, inspiration breath-hold, free breath, breast cancer.

Contributions of each author
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