KARDIOLOGIA POLSKA
Polish Heart Journal
The Official Peer-reviewed Journal of the Polish Cardiac Society since 1957
Online first
This is a provisional PDF only. Copyedited and fully formatted version will be made available soon
ISSN 0022–9032
e-ISSN 1897–4279

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Article type: Short communication

Received: September 7, 2022

Accepted: November 21, 2022

Early publication date: December 4, 2022

Role of global longitudinal strain in evaluating radiotherapy-induced early cardiotoxicity in breast cancer: A meta-analysis

Short title: Role of GLS in evaluating early cardiotoxicity

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INTRODUCTION

The incidence of breast cancer ranks first among all female malignant tumors [1]. Radiotherapy (RT) plays an important role in the management of breast cancer, reducing the risk of local relapse and specific death. However, RT can increase the risk of cardiovascular morbidity and mortality due to the incidental radiation of cardiac structures [2]. The reduction of left ventricular ejection fraction (LVEF) mainly occurs to significant left ventricular dysfunction. It is noteworthy that myocardial function can change greatly without change of LVEF [3].

Global longitudinal strain (GLS) assessed by speckle-tracking echocardiography (STE) is a new technique for detecting and quantifying subtle disturbances in left ventricular systolic function [4]. In this meta-analysis, we aimed to investigate the role of GLS in evaluating radiotherapy-induced early cardiotoxicity in breast cancer.

METHODS

The present study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Two researchers independently conducted a literature search through PubMed, EMBASE, Web of Science, Cochrane Library, wanfang and CNKI databases in January 2010 and March 2022, and the language was limited to Chinese or English. The search words mainly included “Breast Cancer”, “Radiotherapy”, “Cardiotoxicity”, “Echocardiography”, etc.

Inclusion and exclusion criteria

Inclusion criteria: (1) the breast cancer patients received adjuvant RT with or without adjuvant chemotherapy; (2) speckle-tracking echocardiography was performed before radiotherapy and during follow-up and get the result of LVEF and GLS. Exclusion criteria: (1) left and right breast cancer data were not recorded separately; (2) studies were duplicated or data were overlapped; (3) letters, case reports, editorials, or reviews.

Data abstraction

Two investigators independently extracted the following data: study characteristics (authors, year of publication), participant characteristics (age, sample size of different groups, the proportion of using chemotherapy and targeted therapy, radiotherapy dose, whether using cardioprotective agents).

Statistics analysis

Data were entered into RevMan 5.4 software to conduct the meta-analysis and the heterogeneity analysis. Because the change in LVEF and GLS from baseline to post-RT was regarded as continuous data, the weighted mean difference (WMD) and 95% confidence intervals (95% CI) were used to draw Forest plot. A two-sided P-value<0.05 was considered statistically significant in the WMD analysis. The Cochran Q test and I^2 statistics were conducted to assess the heterogeneity of the effects. If P-values >0.1 or I^2 statistics <50% were observed, it can be considered that there was no obvious heterogeneity between studies, and the fixed effects model was used to pool data. If heterogeneity was detected, we conducted subgroup analysis to explore the source of heterogeneity.

RESULTS AND DISCUSSION

Finally, 9 literatures [3, 5–12] were included in meta-analysis. The literature retrieval process is shown in Supplementary material, *Figure S1*, and the basic information of the included literature is shown in Supplementary material, *Table S1*.

The average LVEF fluctuated between 60.9% to 73.3% before radiotherapy and 58.7% to 70.5% after radiotherapy. Merging analysis shown that LVEF after radiotherapy was lower than baseline (–0.98 WMD; 95% CI, –1.88 to –0.08; P = 0.03), and no heterogeneity among studies (I^2 = 13%, P = 0.33, Supplementary material, *Figure S2A*). At 6 months follow-up, the result of LVEF did not change (–0.83 WMD; 95% CI –3.09 to 1.43; P = 0.47), and with no heterogeneity among studies (I^2 = 0%, P = 0.84, Supplementary material, *Figure S2B*). As for the right breast cancer, the LVEF after radiotherapy was no difference (–0.17 WMD; 95% CI –2.07 to 1.72, P = 0.86), and there was no heterogeneity between studies (I^2 = 0%, P = 0.54, Supplementary material, *Figure S3*).

After radiotherapy for left breast cancer, GLS decreased, with average GLS values in the range of –21.4% to –16.0% before radiotherapy and –18.7% to –17.2% after radiotherapy (1.57 WMD; 95% CI, 1.08–2.07; P <0.001). There was no significant heterogeneity among studies (I^2 = 14%; P = 0.32, Figure 1A). GLS was lower than baseline at 6 weeks, 6 months, and 12 months after radiotherapy (1.84 WMD; 95% CI, 1.13–2.55; P <0.001, Figure 1B), (1.04 WMD; 95% CI, 0.35–1.73; P <0.003, Figure 1C), (1.69 WMD; 95% CI, 0.88–2.50; P <0.001, Figure 1D), with no heterogeneity among studies. After radiotherapy for right breast cancer, the result of GLS is as followed (0.18 WMD; 95% CI, –0.55 to 0.91; P = 0.62), and there was no heterogeneity between studies (I^2 = 0%, P = 0.58, Supplementary material, *Figure S4*).

This meta-analysis showed that the LVEF of patients with left breast cancer decreased slightly after radiotherapy, but remained within the normal range, while the LVEF of patients with right breast cancer did not change significantly after radiotherapy. Erven et al. [3] found that the baseline LVEF was lower in patients receiving chemotherapy, compared to the patients of non-chemotherapy. However, the LVEF reduction caused by radiotherapy was basically same, so it did not affect the results of this meta-analysis.

The results also showed that GLS decreased significantly at 6 and 12 months after radiotherapy. Heggemann et al. [12] showed that GLS was still lower than baseline at 24 months after radiotherapy, but better than 6 months after radiotherapy. Excepted GLS, global myocardial deformation indices also include global radial (GRS) and circumferential strain (GCS). Stokke [13] showed that GLS was the first to be affected in many physiological and pathological processes, possibly because most of the longitudinal fibers were located in the subendocardium that was most vulnerable to be damaged. Maybe it's not enough to focus on the global change. Walker [4] focused on regional myocardial function, and suggested that the longitudinal strain change may be more relevant in the endocardial layer, in particular in the most exposed areas of the left ventricle, corresponding to the apical region and the left anterior descending artery (LAD) territory. Tuohinen et al. [7] study in which patients with left-sided breast cancer experienced apical and global decline, whereas patients with right-sided breast cancer showed basal changes with no changes in GLS. In the future, we need conduct more studies to verify. After all, early recognizing radiation-induced heart disease and early applicating cardioprotective agents were critical to improving the quality of life of breast cancer survivors [14, 15].

Limitations of this meta-analysis: (1) the time of assessing during radiotherapy and follow-up was inconsistent, which may have some influence on the detection of myocardial changes; (2) differences in delineation method and dose limitation of cardiac target in different centers also lead to differences in myocardial changes; (3) the research came from different centers, and different instruments were used for STE detection; (4) the follow-up time is inconsistent; (5) only two studies consider the impact of using cardioprotective agents.

In conclusion, GLS is a good parameter to find early radiation-induced heart disease in left-side breast cancer. As for right-side breast cancer, the segmental changes may be more important.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: None declared.

Funding: None.

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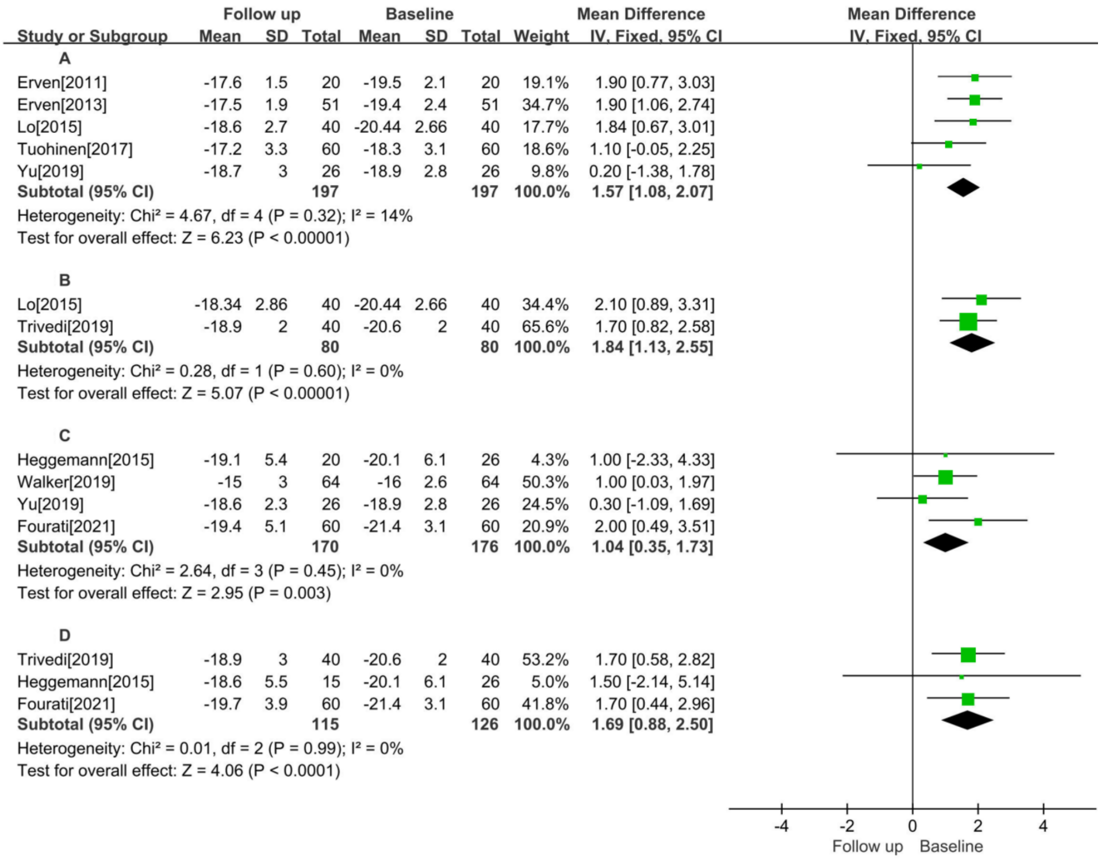

Figure 1. A. GLS changes in left breast cancer before and after radiotherapy. **B.** GLS changes in left breast cancer at 6 weeks after radiotherapy. **C.** GLS changes in left breast cancer at 6 months after radiotherapy. **D.** GLS changes in left breast cancer at 12 months after radiotherapy

Abbreviation: GLS, global longitudinal strain