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

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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 incidental radiation of cardiac structures [2]. The reduction of left ventricular ejection fraction (LVEF) mainly leads to significant left ventricular dysfunction. It is noteworthy that myocardial function can change greatly without any decline in 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-Analysis. 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*

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

### *Data extraction*

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

### *Statistics analysis*

Data were entered into RevMan 5.4 software to conduct the meta-analysis and heterogeneity analysis. Since 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 a forest plot. A two-sided *P*-value <0.05 was considered statistically significant in the WMD analysis. Cochran's 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

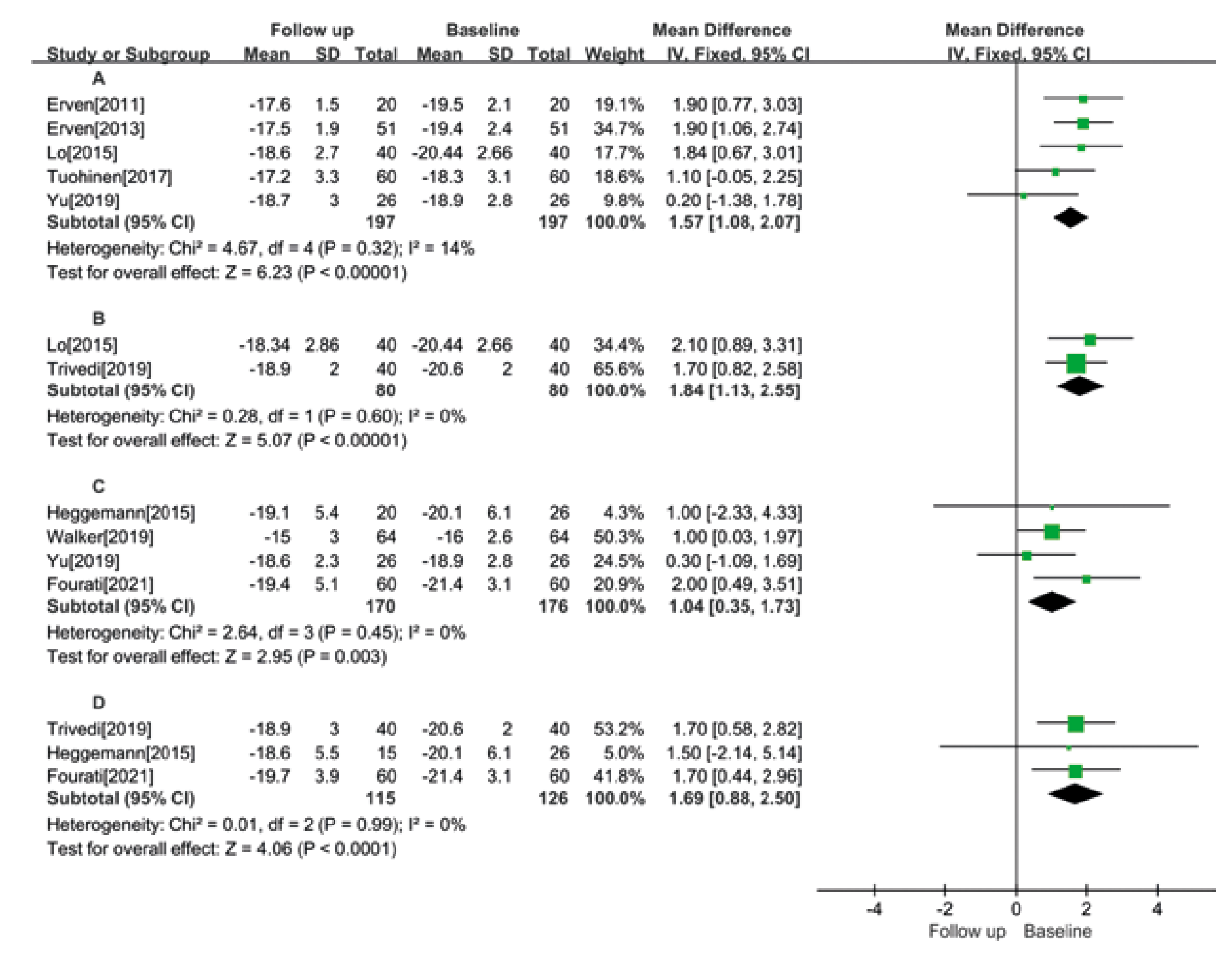


**Figure 1. A.** GLS changes in left-breast cancer before and after radiotherapy. **B.** GLS changes in left-breast cancer at 6 weeks after radiotherapy. **C.** GLS changes in left-breast cancer at 6 months after radiotherapy. **D.** GLS changes in left-breast cancer at 12 months after radiotherapy

Abbreviation: GLS, global longitudinal strain

heterogeneity between studies, and a 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 articles [3, 5–12] were included in the 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 ranged between 60.9% to 73.3% before radiotherapy and 58.7% to 70.5% after radiotherapy. Merging analysis showed that LVEF after radiotherapy was lower than baseline (–0.98 WMD; 95% CI, –1.88 to –0.08; $P = 0.03$), and there was no heterogeneity among studies ($I^2 = 13\%$, $P = 0.33$, Supplementary material, *Figure S2A*). At 6 months of follow-up, the results of LVEF did not change (–0.83 WMD; 95% CI –3.09 to 1.43; $P = 0.47$), with no heterogeneity among studies ($I^2 = 0\%$, $P = 0.84$, Supplementary material, *Figure S2B*). As for the right breast cancer, LVEF after radiotherapy was not different (–0.17 WMD; 95% CI –2.07 to 1.72, $P = 0.86$), and there was no heterogeneity among 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 was 0.18 WMD; 95% CI, –0.55 to 0.91; $P = 0.62$, and there was no heterogeneity among studies ($I^2 = 0\%$, $P = 0.58$, Supplementary material, *Figure S4*).

This meta-analysis showed that LVEF of patients with left breast cancer decreased slightly after radiotherapy but remained within the normal range, while LVEF of patients with right breast cancer did not change significantly after radiotherapy. Erven et al. [3] found that baseline LVEF was lower in patients receiving chemotherapy compared to the patients not receiving chemotherapy. However, LVEF reduction caused by radiotherapy was the 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] demonstrated that GLS was still lower than baseline at 24 months after radiotherapy but better than 6 months after radiotherapy. Except for GLS, global myocardial deformation indices also include global radial (GRS) and circumferential strain (GCS). Stokke [13] showed that GLS was the first marker to be affected in many physiological and pathological processes, possibly because most of the longitudinal fibers were located in the subendocardium which was most vulnerable to damage. Perhaps it is not enough to focus on 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. In a study by Tuohinen et al. [7], 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 to conduct more studies to confirm these observations. After all, early recognition of radiation-induced heart disease and early use of cardioprotective agents were critical to improving the quality of life of breast cancer survivors [14, 15].

Limitations of this meta-analysis include (1) the time of assessment 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 targets in various centers also lead to differences in myocardial changes; (3) the research came from various centers, and different instruments were used for STE detection; (4) the follow-up time was inconsistent; (5) only two studies considered the impact of cardioprotective agents.

In conclusion, GLS is a good parameter to identify 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*

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