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The Effect of External Radiotherapy to the Left Ventricle Systolic Function in Locally Advanced Breast Cancer Patients

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ABSTRACT

Background: Locoregional management in breast cancer patients includes surgery and radiation. Radiation increases the risk of the decreasing of cardiac ventricular performance and known as cardiotoxicity. This study aims to analyze the relationship between radiation exposure in locally advanced breast cancer patients with the left ventricular systolic function.
Methods: The subjects in this study were patients with locally advanced breast cancer who underwent external radiation therapy after surgery procedure at Dr. Soetomo General Hospital in January 2021 - April 2021. Examination of left ventricular performance parameters was carried out using an invasive method, the transthoracic echocardiography. The performance parameters examined were left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS).
Results: A total of 45 patients were recruited in this study. Twenty-two patients (22/45; 48.9%) underwent radiation therapy from the left side and 23 patients (23/45; 51.1%) from the right side. After external radiation, the number of patients with left ventricular dilatation were increased. On the left side, there were 6 patients (6/22; 27.6%) who experienced dilatation compared to before radiation (3 patients), while on the right side of the body there were 8 patients (8/22; 34.8%) who experienced dilatation compared to before radiation (6 patients). There was an increase in the number of patients who experienced a decrease in EFT and EFB after radiation, although the association was not significant. Almost all patients experienced a decrease in GLS values after radiation (44/45; 97.8%).
Conclusion: There was an increase in the number of patients with left ventricular dilatation and decrease in EFT and EFB values after external radiation. Decreased GLS values were found in almost all patients who underwent external radiation in this study.

***Keywords*:** Radiation, locally advanced breast cancer, LVID, ejection fraction, GLS

INTRODUCTION

Breast cancer is the leading cause of death in women and the second leading cause of death from all cancer cases, with an incidence of 11.6% of all types of cancer. The incidence of new breast cancer in 2018 reached 2 million people globally (11.6% of all cancer cases), with an estimated mortality of 600,000 people (6.6%).(1) Global Cancer Observatory data published in 2018 showed that new cases of breast cancer in Indonesia were estimated at 30.9% or approximately 58,256 of 188,231 cases per year (GLOBOCAN, https://gco.iarc.fr/).

Management of patients with breast cancer includes locoregional and systemic management. Locoregional treatment

includes surgery and radiation, while systemic treatment includes chemotherapy, targeted therapy and hormonal therapy. Breast cancer therapy, either chemotherapy or radiation increases the risk of decreased cardiac ventricular performance due to cardiotoxicity mechanism. One of the commonly used marker is the changes in| the left ventricular ejection fraction (LVEF). The decrease in LVEF is assumed to be an early sign of possible cardiotoxicity, but unfortunately the threshold value for clinical decisions varies depending on guidelines and practicing medical practitioners.(2, 3) To validate differences in LVEF cut-off values in various guidelines and as an effort to reduce intra-personal variability, global longitudinal strain (GLS) is recommended as a parameter of left ventricular systolic dysfunction. In contrast to the LVEF obtained by two and/or three-dimensional (2D/3D M-mode) methods, the GLS obtained by speckle tracking of the left ventricle is more capable of early and accurate detection of systolic dysfunction.(3-5)

Currently, the research on the effect of external radiation exposure on the incidence of cardiotoxicity in locally advanced breast cancer patients in Indonesia is still limited. Therefore, it is necessary to conduct research on the effect of external radiation exposure on the incidence of cardiotoxicity. In this study, we aimed to examined the association between external radiation to the left ventricular systolic function in locally advanced breast cancer patients

MATERIALS & METHODS

Study participants

We recruited a total of 45 breast cancer patients who underwent external radiation therapy after surgery procedure at Dr. Soetomo General Hospital (Surabaya, Indonesia) in January 2021 – April 2021. Patients' information such as name, age, address, and telephone number were recorded. Each patient was explained about the study and asked to sign the informed consent as an agreement to participate in the study. Ethical approval was obtained from the Ethics Committee of Dr. Soetomo General Hospital (Surabaya, Indonesia) following the guidelines of the Declaration of Helsinki.

Echocardiography

Echocardiography was performed to examine the left ventricular systolic function. The echocardiography parameters used to determine the left ventricle function in this study were left ventricular internal dimension (LVID), ejection fraction (EF), and global longitudinal strain (GLS). The ejection fraction was measured using 2 methods: ejection fraction Teich (EFT) and ejection fraction biplane (EFB). Echocardiography was performed before the external radiation and 2 – 3 weeks after external radiation.

Statistical Analysis

The statistical analysis in this study was performed using the IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). Discrete variables were tested using the Chi-square test. The degree of association between to variables was measured using Spearman rank correlation coefficient test. Statistical significance was determined when the P value was less than 0.05.

RESULT

Distribution of external radiation locations by age

In this study, we analyzed the distribution of external radiation locations based on age group (Table 1). The total number of patients who underwent external radiation on the left body side of the body was almost equal to the number of patients who underwent external radiation on the right body side (22/45; 48.9% vs. 23/45; 51.1%). Most of the patients were in the 40 – 49 years age group (23/45; 51.1%), whereas there were only 3 patients in the ≥60 years age group.

Table 1. Distribution of external radiation locations by age

Age group	External radiation location	
	n Sinistra (%)	n Dextra (%)
Total	22	23
30-39	5 (22.7)	3 (13.0)
40-49	12 (54.5)	11 (47.8)
50-59	4 (18.2)	7 (30.4)
≥60	1 (4.5)	2 (8.7)

Association between external radiation location and LVID

The association between the location of radiotherapy and the patient's LVID before external radiation (LVID PRE) and after external radiation (LVID POST) is shown in Table 2. On LVID examination the patient is classified as having left ventricular dilatation if the results showed more than 5 cm in internal diameter. In patients undergoing therapy on the left side of the body, the results of the LVID PRE examination showed that there were 19 patients (19/22; 86.4%) with normal results and there were 3 patients (3/22; 13.6%) with dilatation, while in patients who underwent therapy on the right side of the body, the results of the LVID PRE examination showed that there were 23 patients (17/22; 73.9%) with normal results and there were 6 patients (6/22; 26.1%) with dilatation results.

After external radiation, the number of patients with left ventricular dilatation increased in patients underwent external radiation in both left and right body side. After radiation to the left side of the body, there were 6 patients (6/22; 27.6%) who experienced dilatation compared to the previously 3 patients. Meanwhile, after radiation to the right side of the body, there were 8 patients (8/22; 34.8%) who had dilatation compared to the previously 6 patients. From these results it can be concluded that there was an increase in the number of patients experiencing left ventricular dilatation, however, there were no statistically significant association between the location of external radiation and the LVID results of patients before and after external radiation (P = 0.297 and P = 0.587, respectively).

Table 2. Relationship between radiotherapy location and LVID before and after radiation

Location	Total n	LVID PRE (%)		P Value	LVID POST (%)		P Value
		Normal	Dilated		Normal	Dilated	
Sinistra	22	19 (86.4)	3 (13.6)	0.297	16 (51.6)	6 (27.3)	0.587
Dextra	23	17 (73.9)	6 (26.1)		15 (65.2)	8 (34.8)	

LVID: left ventricle internal dimension; LVID PRE: LVID before radiation; LVID POST: LVID after radiation

Association between external radiation location and EFT

Table 3 shows the results of the analysis of the relationship between the external radiation location and the EFT before radiation (EFT PRE) and EFT after radiation (EFT POST). In patients who underwent radiation on the left side of the body, the EFT PRE examination showed that there were 5 patients who experienced a decrease in EFT, while on the right side there were 9 patients who experienced a decrease in EFT. However, after external radiation, there was an increase in the number of patients who experienced a decrease in EFT, consisted of 7 patients who underwent radiation on the left body side and 9 patients who underwent radiation on the right body side. Chi-square analysis showed that there was no significant association between external radiation location and EFT PRE and EFT POST (P = 0.235 and P = 0.608, respectively).

Table 3. Relationship between radiotherapy location and EFT before and after radiation

Location	Total n	EFT PRE (%)		P Value	EFT POST (%)		P Value
		Normal	Decreased		Normal	Decreased	
Sinistra	22	17 (77.3)	5 (22.7)	0.235	15 (68.2)	7 (31.8)	0.608
Dextra	23	14 (60.9)	9 (39.1)		14 (60.9)	9 (39.1)	

EFT: ejection fraction Teich; EFT PRE: EFT before radiation; EFT POST: EFT after radiation

Association between external radiation location and EFB

Table 4 shows the results of the analysis of the relationship between the external radiation location and the EFB before radiation (EFB PRE) and EFB after radiation (EFB POST). In patients who underwent radiation on the left side of the body, EFB PRE examination showed that there were 4 patients who experienced a decrease in EFT, while on the right side there were 5 patients who experienced a decrease in EFT before radiation was given. However, after external radiation, there was an increase in the number of patients who experienced a decrease in EFT, consisted of 8 patients who underwent radiation on the left side and 10 patients who underwent radiation on the right side of the body. Chi-square analysis showed that there was no significant association between external radiation location and EFB PRE and EFB POST (P = 0.766 and P = 0.626, respectively).

Table 4. Relationship between radiotherapy location and EFB before and after radiation

Location	Total n	EFB PRE (%)		P Value	EFB POST (%)		P Value
		Normal	Decreased		Normal	Decreased	
Sinistra	22	18 (81.8)	4 (18.2)	0.766	14 (63.6)	8 (36.4)	0.626
Dextra	23	18 (78.3)	5 (21.7)		13 (56.5)	10 (43.5)	

EFB: ejection fraction biplane; EFB PRE: EFB before radiation; EFB POST: EFB after radiation

Association between LVID and EFT

The association between LVID (PRE and POST) to EFT is shown in Table 5. In general, there is a significant relationship between LVID and EFT POST (P < 0.0001). In the group of patients with normal LVID PRE examination results, there was an increase in the number of patients with decreased EFT results after radiation from 5 patients (5/36; 13.9%) to 7 patients (7/36; 19.4%). In the group of patients with normal LVID results after radiation (LVID POST), there was an increase in the number of patients with decreased EFT results after radiation from 2 patients (2/31; 6.5%) to 3 patients (3/31; 9). ,7%). Meanwhile, in the group of patients with dilated LVID after radiation (LVID POST) results, there was an increase in the number of patients with decreased EFT results after radiation from 12 patients (12/14; 85.7%) to 13 patients (13/14; 92.9%). Spearman's analysis showed that there was a significant relationship between LVID measurement after radiation (LVID POST) and EFT after radiation (EFT POST) (P < 0.0001, r = -0.810)

Table 5. Relationship between LVID and EFT before and after radiation

Echocardiography parameter	EFT PRE			EFT POST		
	Total n	Normal (%)	Decreased (%)	Total n	Normal (%)	Decreased (%)
LVID PRE						
Normal	36	31 (86.1)	5 (13.9)	36	29 (80.6)	7 (19.4)
Dilatasi	9	0 (0.0)	9 (100)	9	0 (0.0)	9 (100)
LVID POST						
Normal	31	29 (93,5)	2 (6,5)	31	28 (90,3)	3 (9,7)
Dilatasi	14	2 (14,3)	12 (85,7)	14	1 (7,1)	13 (92,9)

LVID: left ventricle internal dimension; LVID PRE: LVID before radiation; LVID POST: LVID after radiation; EFT: ejection fraction Teich; EFT PRE: EFT before radiation; EFT POST: EFT after radiation

Association between LVID and EFB

The association between LVID (PRE and POST) to EFB is shown in Table 6. There was a significant association between LVID PRE and EFT POST (P < 0.0001). In the group of patients with normal LVID PRE examination results, there was an increase in the number of patients with decreased EFT results after radiation from 5 patients (5/36; 13.9%) to 7 patients (7/36; 19.4%). In the group of patients with normal LVID examination results after radiation (LVID POST), there was an increase in the number of patients with decreased EFT results after radiation from 3 patients (3/36; 8.3%) to 9 patients (9/36; 25 ,0%). In the group of patients with normal LVID examination results after radiation (LVID POST), there was an increase in the number of patients with decreased EFT results after

radiation from 2 patients (2/31; 6.5%) to 5 patients (5/31; 16 ,1%). Meanwhile, in the group of patients with dilated LVID after radiation (LVID POST) results, there was an increase in the number of patients with decreased EFT results after radiation from 7 patients (7/14; 50.0%) to 13 patients (13/14; 92.9%). Spearman's analysis showed that there was a significant relationship between the results of the LVID measurements after radiation (LVID POST) and the results of the EFT measurements after radiation (EFT POST) ($P < 0.0001$, $r = -0.804$). Table 6. Relationship between LVID and EFB before and after radiation

Table 6. Association between LVID and EFB

Echocardiography parameter	EFB PRE			EFB POST		
	Total n	Normal (%)	Decreased (%)	Total n	Normal (%)	Decreased (%)
LVID PRE						
Normal	36	33 (91.7)	3 (8.3)	36	27 (75.0)	9 (25.0)
Dilatasi	9	3 (33.3)	6 (66.7)	9	0 (0.0)	9 (100)
LVID POST						
Normal	31	29 (93.5)	2 (6.5)	31	26 (83.9)	5 (16.1)
Dilatasi	14	7 (50.0)	7 (50.0)	14	1 (7.1)	13 (92.9)

LVID: left ventricle internal dimension; LVID PRE: LVID before radiation; LVID POST: LVID after radiation; EFB: ejection fraction biplane; EFB PRE: EFB before radiation; EFB POST: EFB after radiation

Analysis of GLS results before and after radiation

We analyzed the distribution of patients' GLS values before radiation (GLS PRE) and after external radiation (GLS POST) based on external radiation location (Table 7). By analyzing the difference between GLS before and after radiation, we found that the difference in GLS values was in the range of -8.55 – 2.00. Of 45 patients, 44 patients (97.8%) had a smaller GLS POST value than the GLS PRE and there was only 1 patient (2.2%) who had higher GLS POST result than GLS PRE. This shows that in the majority of patients had decreased left ventricular function from the aspect of how short the longitudinal heart muscle is during systolic phase. There was a significant difference in GLS between radiation on the right and left sides with $P = 0.017$.

Table 7. Profile of GLS values differences based on location

Echocardiography parameter	Location	n	Mean	Standard Deviation	P Value
GLS differences	Sinistra	22	-3.44	2.230	0.017
	Dextra	23	-1.36	1.363	

GLS: global longitudinal strain

DISCUSSION

In this study, we aimed to analyze the relationship between external radiation exposure and left ventricular systolic function. Previous studies reported that patients who underwent radiation had decreased left ventricular systolic function.(6, 7) In this study we found that in general, the number of patients with decreased left ventricular function was increased after the eternal radiation therapy. The first parameter we analyzed was the LVID or left ventricular internal dimension. Normal LVID is generally in the 2-5 cm range and 5 cm was generally accepted as cut off to determine dilatation in women. Therefore, in this study we used a cutoff value of 5 cm to determine the presence of ventricular dilatation and patients with LVID values of more than 5 cm were defined as subjects with left ventricular dilatation. The data we obtained show that in general there is an increase in the number of patients experiencing left ventricular dilatation after external radiation, both in the group of patients who received radiation on the left side of the body and on the right side of the body, although there was no significant increase in the number. This result was in concordance with previous study that showed an increase LVID value or left ventricle hypertrophy in patients after radiation.(8, 9) Either low dose or high dose of radiation has been reported to cause

cardiac tissue remodeling in mice model tissues.(10) In addition, the occurrence of chain mechanisms in tissue can also cause cardiotoxicity effects that have an effect on tissue structure and increase ventricular dimensions.(11, 12)

Another echocardiography parameter that we analyzed in this study was the ejection fraction (EF). Ejection fraction is commonly calculated using 2 methods, namely ejection fraction Teich (EFT) and ejection fraction biplane (EFB). Both are parameters describing how big the left ventricular ejection fraction is. Interestingly, in this study we also obtained results that is in concordance with previous studies, where patients who underwent external radiation had decreased EFT value although not statistically significant. In total there were only an additional 2 patients who experienced a decrease in EFT. Both patients with decreased EFT underwent radiation to the left side of the body. However, in calculating the ejection fraction using the biplane method, it was found that more patients had decreased ejection fraction, where the number of patients who experienced a decrease in the EFB value was doubled both in the group that received radiation on the left and right sides of the body. This phenomenon can be caused by the cardiotoxicity effect of radiation on the cells or tissues in the heart. Radiation exposure to the heart has the potential to cause inflammation of the microvascular endothelium in the heart so that it can cause a decrease in heart performance, and can even cause heart failure.(13) Statistical analysis showed a significant relationship between LVID values with EFT and EFB. The LVID value, which is a direct parameter of heart dimensions, is reported to have an effect on the quality of the ejection fraction of the left ventricle. In general, an increase in the LVID value which represents cardiac dilatation is considered to have an effect on the non-optimum ejection fraction, which is indicated by a decrease in the EFT and EFB values.(14)

In addition, in this study we also analyzed the relationship of GLS to radiation. Our data showed that almost all patients who underwent radiation had decreased GLS values. Our result was in line with previous researches which stated that there was a negative relationship between radiation and GLS values.(15) The decreased GLS values may resulted in the decreasing ejection fraction of the left ventricle. Therefore, it is important to consider the effect of radiation to left ventricle systolic function.

There are several limitations in this study. First, the relatively small number of samples can affect the power of statistical analysis. Second, the sample obtained is a sample obtained from one hospital, so that the data presented in this study cannot be used to generalize the situation to a larger population. Further research considering a larger sample size can be carried out in the future to provide a clearer picture of the population.

CONCLUSION

There was an increase in the number of patients with left ventricular dilatation and decrease in EFT and EFB values after external radiation. Decreased GLS values were found in almost all patients who underwent external radiation in this study.

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