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Echocardiographic Assessment of Ventricular Cardiomyopathy in Patients with Breast Cancer under Trastuzumab Chemotherapy

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ABSTRACT

Objective(s): Breast cancer is the most common cancer and the leading cause of cancer-related death among women worldwide. Breast cancer treatment has been improved by the development of targeted chemotherapies such as antibodies against HER2 receptors and now Trastuzumab is the standard treatment for HER2 positive breast cancer. Cardiotoxicity is the most prominent adverse effect of Trastuzumab that restricts the usage of this drug. This study is designed to assess cardiomyopathy in patients with breast cancer under Trastuzumab chemotherapy with special respect to both right and left ventricles.

Methods: A total number of 38 cases were evaluated. Echocardiography was done at the baseline and three to six months after the initiation of Trastuzumab chemotherapy.

Results: According to the second echocardiography 24 cases (63.8%) developed cardiotoxicity based on decrease in ejection fraction or decrease in the absolute value of the left and/or right ventricular Global Longitudinal Strain (LV and/or RV GLS). There was a significant difference between the mean values of echocardiographic indices including RVSm, RV Tei-index, LV Tei-index, RV GLS, LV GLS, LVEF, MAPSE, and TAPSE before and after chemotherapy (the p-value for comparison of MAPSE was 0.006, and the p-value for comparison of other parameters was <0.001). There was no significant difference in terms of cardiotoxicity between the group that received radiotherapy in addition to chemotherapy and the group that did not receive radiotherapy.

Conclusion: In conclusion, the best way to minimize Trastuzumab-induced cardiotoxicity is intensive follow-up by echocardiography to detect cardiac impairments in the early stages. Also, the study demonstrated the uniqueness of longitudinal strain especially LV-GLS for early detection of cardiotoxicity.

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Introduction

Breast cancer is the most common cancer and the leading cause of cancer-related death among women worldwide (1, 2). Approximately, one in eight women will develop breast cancer during life (1). Overexpression of human epidermal growth factor receptor 2 (HER2) is detected in about 20 percent of breast cancers which is associated with more aggressive disease, but, higher sensitivity to cytotoxic drugs (3-5).

Breast cancer treatment has been altered by the development of targeted chemotherapies such as antibodies against HER2 receptors (4).

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Trastuzumab is a humanized monoclonal antibody that binds to the extracellular component of HER2 receptor. Previously, diagnosis of HER2-positive breast cancer was accompanied by a lower survival rate and higher risk of metastasis. Today, with the introduction of HER2-targeted therapies like Trastuzumab as the standard treatment there is a significant improvement in clinical outcomes (6, 7). Although Trastuzumab has dramatically amended HER2 breast cancer prognosis and various trials have shown a high safety profile, cardiotoxicity remains the most prominent adverse effect and sometimes restricts the usage of this drug. The exact mechanism of Trastuzumab-induced cardiotoxicity is unclear. Induction of oxidative stress and inflammatory process in cardiac muscle are possible mechanisms (8). Trastuzumab cardiotoxicity is known to be reversible since there is no primary myocyte injury and ultrastructural changes to cardiomyocytes that were detected in anthracycline-induced cardiotoxicity, although, an in vivo study has shown ultrastructural changes in mice model and rising concerns about possible long-lasting cardiotoxic effects of Trastuzumab (9, 10). Also, studies have proven that the reversal of cardiac muscle deterioration can be facilitated by Angiotensin Converting Enzyme (ACE) inhibitors and beta-blockers (11, 12). Early stages of Trastuzumab cardiotoxicity are silent and usually are associated with asymptomatic structural changes rather than symptomatic heart failure (13, 14).

Regarding the asymptomatic process of cardiotoxicity, reversible nature of the disease, and available cardioprotective drugs, early detection of cardiac impairment in patients under chemotherapy with Trastuzumab is of great importance. The best and most available method for early detection of cardiotoxicity is echocardiography which can demonstrate cardiac structure and function by ejection fraction, myocardial strain measurements, and several other parameters (14-16). Most studies, evaluating the cardiotoxic effects of Trastuzumab by echocardiography, have focused on left ventricular indices so we aimed to design a study to assess cardiomyopathy in patients with breast cancer under Trastuzumab chemotherapy with special respect to both right and left ventricular cardiomyopathy.

Materials and Methods

Sampling, inclusion criteria, and exclusion criteria

In this study, a group of women with HER2-positive breast cancer was selected by convenience sampling method. Cases were referred from the oncology clinic to a specific cardiology clinic. Then, patients were evaluated by a cardiologist in terms of cardiovascular symptoms, signs, or risk factors. Cases with a history of hypertension, coronary artery disease, cardiomyopathy, heart failure, congenital heart disease, pulmonary embolism, or any predisposing factors for right and left ventricular dysfunction were excluded from the study. Cases were chosen regardless of previous chemotherapy courses, but in case of any cardiovascular symptoms or signs related to previous chemotherapies on examination or first echocardiography, cases were not eligible to enter the study. Also, cases were excluded in case of allergic reaction to Trastuzumab chemotherapy, death before the end of study course and refusal to refer for further evaluations. Finally, 38 cases of women with HER2-positive breast cancer were entered to the study and evaluated after receiving informed consent.

Clinical follow-up of patients

All cases were evaluated on the first visit, before initiation of treatment by physical examination. The patients underwent echocardiography on the first visit, then they were referred to an oncology clinic for initiation of treatment. Eleven cases received Trastuzumab chemotherapy alone and 27 cases received radiotherapy in addition to Trastuzumab chemotherapy. Patients were followed until at least three months after initiation of chemotherapy and radiotherapy. A second cardiologist visit was planned for all patients between three to six months from the first visit and all patients underwent echocardiography for the second time. The results of both echocardiograms were recorded in checklists. The minimum time interval between first and second echocardiography was considered three months since the minimum time interval required for detection of cardiac changes after starting treatment is three months (17, 18).

Echocardiographic evaluation

RVSm (Right Ventricular Systolic velocity), RV Tei-index (Right Ventricle Tei-index), LV Tei-index (Left Ventricle Tei-index), RV GLS (Right Ventricular Global Longitudinal Strain), LV GLS (Left Ventricular Global Longitudinal Strain), LVEF (Left Ventricular Ejection Fraction), MAPSE (Mitral Annular Plane Systolic Excursion), TAPSE (Tricuspid Annular Plane Systolic Excursion), and valvular heart disease were evaluated by echocardiography and recorded for two times. [EPIQ 7 Ultrasound system for cardiology, Philips or GE Vivid S6 Ultrasound Machine] was used

to perform the echocardiographic evaluation. Echocardiography of all patients was done by one person (cardiologist, echocardiography fellowship) in order to minimize inter-personal variations in interpretation. Cardiotoxicity was defined as ≥ 10% reduction in LVEF to less than 50% according to the European Society of Cardiology (ESC) position paper (19). Also, in terms of myocardial strain measurement, the cut-off value for cardiotoxicity was considered as ≥ 15% decrease in absolute value of LV GLS (19) and ≥ 14.8% decrease in absolute value of RV GLS (17). Having any of the above criteria were considered as cardiotoxicity in this study. Trastuzumab was discontinued for patients diagnosed to have chemotherapy-induced cardiotoxicity on the second visit. Also, ACE inhibitors, beta-blockers, and Spironolactone were prescribed to minimize or reverse the cardiotoxic effects.

Statistical methods

The continuous variables were presented as mean and standard deviation and the categorical variables as frequency and percentage. The paired t-test was used to compare echocardiography indices before and after treatment. T-Test was used for comparison of mean age between two groups of patients with and without cardiotoxicity. Chi-2 test was used to compare cardiotoxicity between age (<50 years/ ≥50 years) and treatment (chemotherapy/ chemotherapy and radiotherapy) groups. Change analysis was performed for comparison of differences before and after treatment among two treatment groups and the Mann-Whitney U test was used to evaluate the significance of the relationship. All statistical analyses were conducted at a significance level of 0.05. SPSS software, version 22 was used for data analysis (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp).

Results

In this study, a total number of 38 cases were evaluated. Of whom, 11 cases received Trastuzumab chemotherapy and 27 cases received radiotherapy in addition to chemotherapy. The mean age of participants was 53.21 (±9.01) years with the range of 33 to 70 years and the most common age among participants was 44 years. 34.2% were under 50 years and others were older. The mean age did not have a significant difference between patients who developed cardiotoxicity and patients who did not develop cardiotoxicity (p-value: 0.326).

Regarding the definition of cardiotoxicity in this study [having at least one of the following items: 1- more than 10% reduction in LVEF to less than 50%. 2- more than 15% decrease in the absolute value of LV GLS. 3- more than 14.8% decrease in the absolute value of RV GLS; some cases fulfilled more than one item], a total number of 24 cases (63.8%) developed cardiotoxicity [55.3% based on the first item 57.9% based on the second one, and, 23.7% based on the third one]. There was no significant difference between age (<50 years/ ≥50 years) and treatment (chemotherapy/ chemotherapy and radiotherapy) groups in terms of rate of cardiotoxicity (p-value > 0.05). [Table 1 and 2]

If we consider the conventional criteria of EF reduction as a standard for cardiotoxicity, the cut-

Table 1. Rate of cardiotoxicity among two age groups

		<50 years N (%)	≥50 years N (%)	Total N (%)	p-value of chi-2 test
Cardiotoxicity	**Yes**	10 (26.3%)	14 (36.8%)	24 (63.2%)	0.294
	No	3 (7.9%)	11 (28.9%)	14 (36.8%)	

Table 2. Rate of cardiotoxicity among two treatment groups

		Chemotherapy N (%)	Chemotherapy and Radiotherapy N (%)	Total N (%)	p-value of chi-2 test
Cardiotoxicity	**Yes**	6 (15.8%)	18 (47.4%)	24 (63.2%)	0.712
	No	5 (13.2%)	9 (23.7%)	14 (36.8%)	

Table 3. Mean values for the first and second echocardiogram parameters

		First Echocardiography (Mean ± SD)	Second Echocardiography (Mean ± SD)	p-value for paired t-test
Echocardiography indices	MAPSE (mm)	13.84 ± 3.0	12.47 ± 3.2	0.006
	TAPSE (mm)	19.97 ± 2.5	18.05 ± 3.3	<0.001
	LVEF (percent)	53.54 ± 3.8	49.18 ± 6.1	<0.001
	RVGLS (percent)	-20.00 ± 2.1	-18.37 ± 2.9	<0.001
	LVGLS (percent)	-21.03 ± 3.3	-17.76 ± 3.2	<0.001
	RVTei (ratio)	46.53 ± 11.5	52.92 ± 8.7	<0.001
	LVTei (ratio)	40.37 ± 5.2	47.03 ± 7.6	<0.001
	RVSm (cm/s)	9.84 ± 1.8	8.47 ± 2.2	<0.001

MAPSE: Mitral Annular Plane Systolic Excursion, TAPSE: Tricuspid Annular Plane Systolic Excursion, LVEF: Left Ventricular Ejection Fraction, RV GLS: Right Ventricular Global Longitudinal Strain, LV GLS: Left Ventricular Global Longitudinal Strain, RV Tei-index: Right Ventricle Tei-index, LV Tei-index: Left Ventricle Tei-index, RVSm: Right Ventricular Systolic velocity, mm: millimeter, cm/s: centimeters/second, SD: Standard Deviation

off of 15% decrease in the absolute LV-GLS value will have 88.2% sensitivity and 66.7% specificity for detection of cardiotoxicity. Also, the cut-off of 14.8% decrease in the absolute RV-GLS value will have 52.9% sensitivity and 100% specificity for detection of cardiotoxicity. Further values for LV-GLS are as following: Positive predictive value equal to 68.1%, negative predictive value equal to 87.5%, and likelihood ratio equal to 2.6.

Mean values for the first and second echocardiogram parameters are mentioned in table 3. There was a significant difference between the mean values of the first and second echocardiogram for all of the mentioned parameters including RVSm, RV Tei-index, LV Tei-index, RV GLS, LV GLS, LVEF, MAPSE, and TAPSE. Also, the mean values of echocardiography parameters for each of the age and treatment groups are mentioned in table 4 and table 5.

The comparison of mean differences before

Table 4. Mean values of echocardiography parameters among age groups

			First Echocardiography (Mean ± SD)	Second Echocardiography (Mean ± SD)	p-value for paired t-test
Echocardiography indices	<50 years	MAPSE (mm)	13.08 ± 1.7	11.92 ± 3.0	0.068
		TAPSE (mm)	19.38 ± 2.6	17.62 ± 3.1	<0.001
		LVEF (percent)	53.35 ± 2.6	47.31 ± 7.2	0.016
		RVGLS (percent)	-20.46 ± 1.6	-18.46 ± 3.0	<0.001
		LVGLS (percent)	-22.46 ± 4.5	-17.54 ± 3.7	0.001
		RVTei (ratio)	47.92 ± 8.2	53.08 ± 10.5	0.001
		LVTei (ratio)	43.15 ± 5.4	48.46 ± 6.5	0.009
		RVSm (cm/s)	9.23 ± 2.0	8.15 ± 2.9	0.057
		MAPSE (mm)	14.24 ± 3.4	12.76 ± 3.2	0.033
		TAPSE (mm)	20.28 ± 2.4	18.28 ± 3.5	<0.001
		LVEF (percent)	53.64 ± 4.4	50.16 ± 5.3	0.009

Continued Table 4.

	≥50 years	RVGLS (percent)	-19.76 ± 2.3	-18.32 ± 2.8	0.028
		LVGLS (percent)	-20.28 ± 2.2	-17.88 ± 3.0	<0.001
		RVTei (ratio)	45.80 ± 13.0	52.84 ± 8.0	0.006
		LVTei (ratio)	38.92 ± 4.5	46.28 ± 8.1	<0.001
		RVSm (cm/s)	10.16 ± 1.6	8.64 ± 1.8	0.002

MAPSE: Mitral Annular Plane Systolic Excursion, TAPSE: Tricuspid Annular Plane Systolic Excursion, LVEF: Left Ventricular Ejection Fraction, RV GLS: Right Ventricular Global Longitudinal Strain, LV GLS: Left Ventricular Global Longitudinal Strain, RV Tei-index: Right Ventricle Tei-index, LV Tei-index: Left Ventricle Tei-index, RVSm: Right Ventricular Systolic velocity, mm: millimeter, cm/s: centimeters/second, SD: Standard Deviation

and after treatment among two treatment groups showed that there is no significant difference between the two groups in terms of RVSm, RV Tei-index, LV Tei-index, RV GLS, LVEF, MAPSE, and TAPSE. Only LV GLS changes before and after treatment were significantly different between the two treatment groups (chemotherapy/ chemotherapy and radiotherapy). The decrease in LV GLS absolute value was more severe in the group who received chemotherapy and radiotherapy (p-value: 0.018).

The rate of valvular heart disease was 15.8% among participants and it did not change after treatment.

Table 5. Mean values of echocardiography parameters among treatment groups

			First Echocardiography (Mean ± SD)	Second Echocardiography (Mean ± SD)	p-value for paired t-test
Echocardiography indices	Chemotherapy	MAPSE (mm)	13.18 ± 3.3	12 ± 2.4	0.358
		TAPSE (mm)	20.82 ± 2.0	18.36 ± 2.9	0.002
		LVEF (percent)	54.64 ± 0.8	49.36 ± 5.8	0.019
		RVGLS (percent)	-20.27 ± 1.6	-19.09 ± 2.9	0.174
		LVGLS (percent)	-19.64 ± 3.0	-18.36 ± 3.0	0.181
		RVTei (ratio)	46.91 ± 15.0	49.82 ± 7.4	0.476
		LVTei (ratio)	37.00 ± 4.3	45.18 ± 6.0	<0.001
		RVSm (cm/s)	10.82 ± 1.2	8.64 ± 2.0	0.002
	Chemotherapy & Radiotherapy	MAPSE (mm)	14.11 ± 2.8	12.67 ± 3.5	0.004
		TAPSE (mm)	19.63 ± 2.6	17.93 ± 3.5	<0.001
		LVEF (percent)	53.09 ± 4.5	49.11 ± 6.3	0.007
		RVGLS (percent)	-19.89 ± 2.3	-18.07 ± 2.8	0.001
		LVGLS (percent)	-21.59 ± 3.3	-17.52 ± 3.3	<0.001
		RVTei (ratio)	46.37 ± 10.1	54.19 ± 9.1	<0.001
		LVTei (ratio)	41.74 ± 4.9	47.78 ± 8.1	<0.001
		RVSm (cm/s)	9.44 ± 1.9	8.41 ± 2.3	0.017

MAPSE: Mitral Annular Plane Systolic Excursion, TAPSE: Tricuspid Annular Plane Systolic Excursion, LVEF: Left Ventricular Ejection Fraction, RV GLS: Right Ventricular Global Longitudinal Strain, LV GLS: Left Ventricular Global Longitudinal Strain, RV Tei-index: Right Ventricle Tei-index, LV Tei-index: Left Ventricle Tei-index, RVSm: Right Ventricular Systolic velocity, mm: millimeter, cm/s: centimeters/second, SD: Standard Deviation

Discussion

The presence of HER2 previously was accompanied by the fear of encountering a more aggressive disease, now, in the era of targeted therapy, it promises better treatment response. A humanized monoclonal antibody, named Trastuzumab, has prolonged the survival of HER2-positive breast cancer patients. Despite significant improvement in the prognosis of breast cancer, cardiotoxicity remains the main complication of Trastuzumab therapy. The complication ranges from asymptomatic forms that only can be detected by echocardiography to signification reduction of Ejection Fraction (EF) and heart failure. The susceptibility to cytotoxic drugs varies among individuals based on the special genes affecting metabolism and elimination of the drug and the adverse effects can be controlled by adjusting the dosage and treatment plans, avoidance of other drugs with synergistic cardiotoxic effects, and routine monitoring of cardiotoxicity for in-time detection of treatable complications. Several studies have evaluated the cardiotoxic effects of Trastuzumab and recommend cardiac function assessment by echocardiography before and during Trastuzumab therapy (15, 20). While most of the studies have focused on the left ventricular assessment, here, we evaluated Trastuzumab-induced cardiotoxicity with special respect to both right and left ventricles.

In our study, we evaluated a total number of 38 cases of HER2-positive breast cancer under Trastuzumab chemotherapy. Of whom, 27 cases received radiotherapy in addition to chemotherapy (11 cases only received Trastuzumab chemotherapy). The mean age of participants was 53.2 years. In this study finally, 55.3% developed cardiotoxicity based on the conventional criteria which means more than 10% reduction in LVEF to less than 50%. A similar study by Karamida et al. enrolled 101 women with breast cancer receiving Trastuzumab for 12 months and evaluated the patients by echocardiography at the baseline and every 3 months till one year. In this study, finally 9.9% of cases developed cardiotoxicity based on the same criteria of EF reduction which was significantly lower in comparison to our study. According to the findings of Karamida et al. after three months only LV-EF and LV-GLS were significantly reduced, after six months LV-EF, LV-GLS, and RV-GLS were significantly reduced to their lowest level, after nine months LV-EF again declined in comparison to its previous levels but LV and RV-GLS were unchanged, and finally, at 12 months the mentioned factors were all significantly decreased compared to the baseline, however, in our study all of the measured echocardiography indices were significantly changed after a three-to-six months follow-up period (17). These findings show that we detected cardiotoxicity in a larger group of patients and earlier than in similar studies. Another study by Arciniegas Calle et al. evaluated 66 patients (mean age: 52 years) with breast cancer under Anthracycline-Trastuzumab chemotherapy. All cases had normal pre-treatment EF and were followed by echocardiography after the first and second chemotherapy cycles. Finally, 20% developed cardiotoxicity based on the EF reduction, of whom 46% were detected after the first cycle and 54% after the second chemotherapy cycle. Compared to the baseline, global longitudinal strain (GLS) and global circumferential strain (GCS) after the first and second cycles were significantly reduced ($p<0.01$) even in patients receiving under the upper limit of recommended cardiac safe dosage. The mentioned study has concluded that abnormal results of 2-dimensional speckle tracking echocardiography even with normal EF, can predict further cardiotoxicity and decrease of EF (14). Another study by Nakano et al. evaluated GLS, GCS, and EF among nine women with breast cancer by cardiac magnetic resonance imaging (CMR). Results showed that LV-GLS, LV-GCS, LV-EF, and RV-GCS all decreased significantly after 6 months, however, RV-GLS and RV-EF were unchanged. Finally, the study recommended that LV longitudinal strain is the best parameter to predict cardiotoxicity. This study implicated a new method of evaluating cardiac function by magnetic resonance imaging, although, the sample size was too small. Also, CMR cannot be implicated routinely for patient follow-up due to high costs and limited availability (21).

In our study, we evaluated cardiotoxicity based on three definitions. First, more than 10% reduction in LVEF to less than 50%, and 55.3% of cases fulfilled this definition. Second, more than 15% decrease in the absolute value of LV GLS, and 57.9% of cases fulfilled this definition. Third, more than 14.8% decrease in the absolute value of RV GLS, and 23.7% of cases fulfilled this definition. Totally, 63.8% of cases developed cardiotoxicity based on one of the mentioned criteria. The small difference between percentages of cardiotoxicity based on the first definition, the second definition, and the total percentage shows that these definitions overlap which means that most cases with cardiac function reduction fulfill both definitions (EF reduction and decrease of LV-GLS absolute value).

According to the results of our study the cut-off of 15% decrease in the absolute LV-GLS value has 88.2% sensitivity and 66.7% specificity for the detection of cardiotoxicity. Also, the cut-off of 14.8% decrease in the absolute RV-GLS value has 52.9% sensitivity and 100% specificity for the

detection of cardiotoxicity. The mentioned findings mean that LV-GLS is a better value for predicting cardiotoxicity (regarding its higher sensitivity) but, normal RV-GLS values (in absence of other abnormal parameters) can rule-out right sided cardiotoxicity (regarding 100% specificity). A similar study by Keramida et al. with the same cut-off values for defining cardiotoxicity based on LV and RV-GLS parameters reported 73.3% sensitivity and 78.5% specificity for LV-GLS and 66.7% sensitivity and 70.8% specificity for RV-GLS for prediction of cardiotoxicity (17). The calculated sensitivity and specificity of LV-GLS in the mentioned study are similar to our results.

According to the results of our study, only LV-GLS changes before and after treatment were significantly different between the two treatment groups (chemotherapy/ chemotherapy and radiotherapy) and there was no significant difference for other parameters. The decrease in LV-GLS absolute value was more severe in the group that received chemotherapy and radiotherapy. Also, a similar study reported that a history of previous radiotherapy did not significantly affect the development of cardiotoxicity in patients under Trastuzumab chemotherapy and LV-GLS was the only parameter affected by radiotherapy (17). This study demonstrated similar findings to our study in terms of possible synergistic effects of radiotherapy on Trastuzumab-induced cardiotoxicity although further research is needed for determining the precise effects of radiotherapy.

Conclusion

In conclusion, the significant effect of Trastuzumab chemotherapy on HER2-positive breast cancer is accompanied by its potential cardiotoxic effects. The best way to minimize Trastuzumab-induced cardiotoxicity is intensive follow-up, so that we can detect the cardiac effects in the early stages, discontinue Trastuzumab, and change the treatment plan. One of the best and most cost-effective methods for follow-up is echocardiography. Our study demonstrated the uniqueness of longitudinal strain especially LV-GLS for early detection of cardiotoxicity. Further studies are needed to provide more information about the protective effects of the drugs including Angiotensin converting enzyme (ACE) inhibitors, Beta-Blockers, and Metformin against Trastuzumab cardiotoxicity.

Abbreviations

HER2: Human Epidermal Growth Factor Receptor 2, ESC: European Society of Cardiology, ACE: Angiotensin Converting Enzyme, LV: Left Ventricle, RV: Right Ventricle, EF: Ejection Fraction, RVSm: Right Ventricular Systolic velocity, RV Tei-index: Right Ventricle Tei-index, LV Tei-index: Left Ventricle Tei-index, RV GLS: Right Ventricular Global Longitudinal Strain, LV GLS: Left Ventricular Global Longitudinal Strain, LVEF: Left Ventricular Ejection Fraction, MAPSE: Mitral Annular Plane Systolic Excursion, TAPSE: Tricuspid Annular Plane Systolic Excursion

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Conflicts of Interest

None

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Ethical approval

The study was approved by the ethics committee of Hamadan University of Medical Sciences (IR.UMSHA.REC.1399.170). Cases were entered to the study after receiving informed consent.

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