Rev bras ecocardiogr imagem cardiovasc. 2013;**26**(2):115-120
ISSN 1984 - 3038

CASE REPORT

Multimodality Cardiovascular Imaging in Aortic Valve Lesion Characterization After Radiotherapy: Report of Four Cases

Multimodalidad en Imagen Cardiovascular en la Caracterización de Lesión Valvular Aórtica Pos-Radioterapia: Relato de Cuatro Casos

Eliza de Almeida Gripp[1], Flávia Candolo Pupo Barbosa[2], Marcelo Iorio Garcia[3], Rafael Rabischoffsky[4], Juliana Serafim da Silveira[5], Marcio Reisner[6], Evandro Tinoco Mesquita[7], Arnaldo Rabischoffsky[8]

[1]. Aluna do programa de pós-graduação em Medicina (Cardiologia), em nível de Mestrado pela UFRJ (Universidade Federal do Rio de Janeiro). Especialista em Cardiologia pela Sociedade Brasileira de Cardiologia e Ecocardiografia pela DIC/ DEPECO Departamento de Imagem Cardiovascular/ Departamento de Ecocardiografia. Médica do Serviço de Ecocardiografia do Hospital Pró Cardíaco. Rio de Janeiro-RJ – Brasil-BR [2]. Mestre em Cardiologia pela Universidade Federal Fluminense. Especialista em Cardiologia pela Sociedade Brasileira de Cardiologia. Médico do Serviço de Ecocardiografia do Hospital Pró Cardíaco. Rio de Janeiro-RJ – Brasil-BR [3]. Doutor em Cardiologia pela Universidade Federal do Rio de Janeiro. Médico do Serviço de Ecocardiografia do Hospital Pró Cardíaco. Rio de Janeiro-RJ – Brasil-BR [4]. Residente de Cardiologia do Hospital Pró Cardíaco. Rio de Janeiro-RJ – Brasil-BR [5]. Radiologista do Serviço de Pesquisa Clínica do Instituto Nacional do Câncer e do Serviço de Radiologia do Hospital Pró Cardíaco. Rio de Janeiro-RJ – Brasil-BR [6]. Doutor em Medicina pela Universidade Federal do Rio de Janeiro. Médico Radioterapêutico do Hospital Universitário Clementino Fraga Filho e das Clínicas Oncológicas Integradas. Rio de Janeiro-RJ – Brasil-BR [7]. Doutor em Cardiologia pela Universidade de São Paulo. Professor Adjunto da Universidade Federal Fluminense. Diretor Clínico do Hospital Pró Cardíaco. Rio de Janeiro-RJ – Brasil-DF [8]. Coordenador do Serviço de Ecocardiografia do Hospital Pró Cardíaco. Rio de Janeiro-RJ – Brasil-BR

SUMMARY

Treatment efficacy of tumors like Hodgkin's Lymphoma and breast cancer with the use of radiotherapy has significantly reduced morbidity and mortality of these patients. However, with the increase of survival, cardiovascular complication, e.g., valvar lesions has arisen years to decades after the end of radiotherapy. The following with echocardiography after radiotherapy is an essential step in early detection and following, because of low cost and easy access. The aim of this paper is to report four cases of patients that developed aortic valvar lesion after radiotherapy.

Descriptors: Echocardiography, Doppler; Heart Neoplasms/complications; Radiotherapy/complications; Heart Valve Disease; Aortic Valve Stenosis

RESUMEN

La eficacia del tratamiento de tumores como linfoma Hodgkin y cáncer de mama con el uso de radioterapia redujo significativamente la morbilidad y mortalidad de esos pacientes. Todavía, con el aumento de la sobrevida, las complicaciones cardiovasculares, entre ellas, las lesiones valvulares comenzaron a surgir, años o hasta décadas después de la radioterapia. El acompañamiento con el ecodopplercardiograma, después de la radioterapia, es indispensable como medida de detección precoz y acompañamiento evolutivo, debido a su bajo costo y fácil acceso. El objetivo de este estudio es relatar cuatro casos de pacientes que desarrollaron lesión valvular aórtica después de la radioterapia.

Descritores: Ecocardiografía Doppler, Neoplasias Cardíacas/complicaciones, Radioterapia/complicaciones, Enfermedades de las Válvulas Cardíacas, Estenosis de la Válvula Aórtica

Institution: Hospital Pró-Cardíaco; Rio de Janeiro, RJ-Brasil. BR
Mail: Rua Belisário Távora, nº 211/403 Laranjeiras 22245-070 Rio de Janeiro- RJ – Brasil-BR elizagripp@yahoo.com.br
Received on: 02/07/2012 - **Accepted on:** 06/08/2012

Introduction

The use of radiotherapy has significantly increased the survival of patients with Hodgkin lymphoma and breast cancer, but a new condition has emerged: valve disease associated to radiotherapy (VDAR), whose actual prevalence is not known[1].

Studies have shown that thoracic irradiation triggers an inflammatory process, thickening, and progressive valve fibrosis years after the treatment[2]. The absence of early valve disease after radiotherapy does not mean low risk to late development[3].

In addition to addressing cardiovascular complications after radiotherapy, the First Brazilian Guideline for Cardio-Oncology4 also addresses valve diseases. The aortic valve disease is the most common one due to its proximity to the radiation field. Its prevalence increases compared to the time interval from radiation, as well as the severity of the lesion. The total dose of radiation, the size of the irradiated field and the concomitant use of chemotherapy (anthracyclines) associated to cumulative dose increase the risk of cardiovascular changes[1,3]. Irradiation may also cause lesions in the myocardium, pericardium, coronary arteries and conduction system.

Four cases of aortic valve lesion due to radiotherapy are reported below, experienced in the echocardiography service of an outsourced cardiovascular imaging center.

Case Report

Case 1: C.A.A., 56 years old, male, diagnosed with Hodgkin lymphoma when he was 13 years old (1969). Doppler echocardiogram was performed before and after treatment with no changes. Treatment included doxorubicin and mantle field radiotherapy. In 2005, when he was 49 years old, Doppler echocardiogram showed thickened tricuspid aortic valve with calcification, mild stenosis (mean gradient = 23 mm Hg), and mild reflux. Simpson ejection fraction (EF) = 65%. Computer tomography of the thorax with no contrast showed aortic valve calcification.

In 2011, when he was 55 years old, he had hypertension and reported being tired on moderate exertion. We underwent cardiac catheterization and successful right coronary angioplasty, which had 75% obstruction. However, symptoms did not resolve. At physical examination, a 3+/6 systolic murmur was detected in the aortic area. Doppler echocardiogram showed severe aortic stenosis, mean gradient = 43 mmHg, valve area (VA) = 0.9 cm^2, with mild to moderate reflux. Simpson ejection fraction (EF) = 60%. Left ventricle/body surface (BS) mass 98 g/m^2 (normal up to 115 g/m^2). Valve replacement was indicated to the patient. He underwent surgery with mechanical prosthesis implant in 2012. Patient evolved in functional class I (Figure 1).

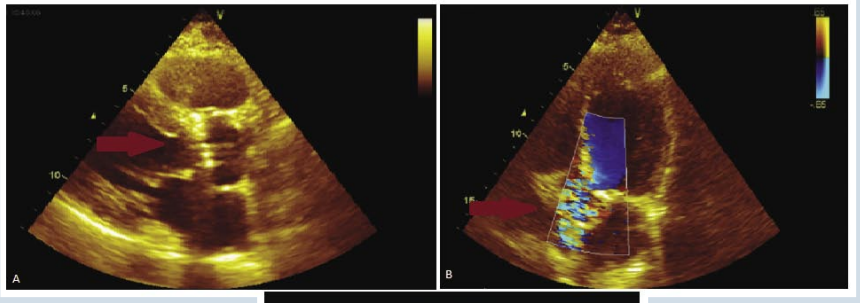

Image A: Doppler echocardiogram, longitudinal parasternal view, showing thickening and significant calcification of the aortic valve.

Image B: Apical 5-chamber view showing turbulence through the aortic valve. This confirmed aortic stenosis

Image C: Computer tomography, coronal plane, with no contrast confirmed aortic valve calcification (arrow).

Figure 1: Patient C.A.A. subjected to Doppler echocardiogram and computer tomography.

Case 2: C.M.P., female, 53 years old, hypertension, treated with chemotherapy and radiotherapy due to rhabdomyosarcoma of the mediastinum when she was 34

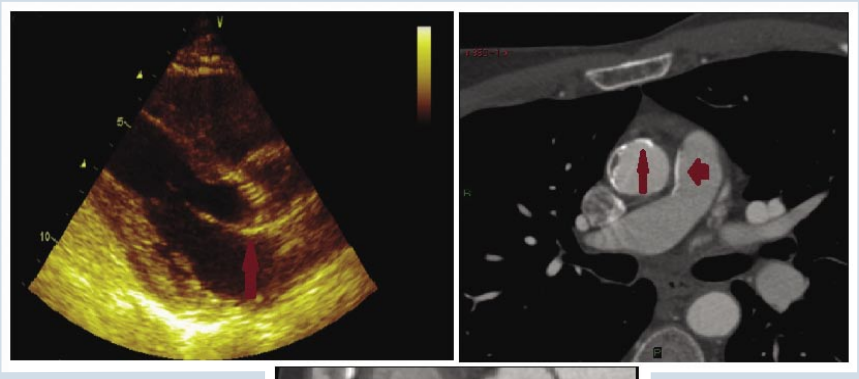

Image A:
Longitudinal parasternal view showing aortic valve thickening.

Image C:
Coronary artery angiotomography: multiplanar curved reconstruction of the right coronary showing calcifications in the coronary ostium (thin arrow) and aortic valve (thick arrow). Total calcium score = 121 (Agatston), at the 90% percentile for age range and gender.

Image B:
Computer tomography with no contrast at cardiac bottom vessels showed significant parietal calcification of the ascending aorta (thin arrow) and of the pulmonary aorta trunk (thick arrow).

Figure 2: Patient R.C. subjected to Doppler echocardiogram and computer tomography.

years old (1992). She underwent myocardial revascularization ten years ago (2002). Surgery records mentioned it was easy to access coronary vessels. Pre-operative Doppler echocardiogram was performed and showed thickening of the tricuspid aortic valve and mild stenosis (mean gradient = 9 mmHg, VA = 1.6 cm^2, left ventricle/body surface mass = 83 g/m^2). Simpson EF = 50%. Currently, the patient is in functional class II, with mild left ventricular dysfunction, severe stenosis, mean gradient = 40 mmHg, VA = 0.6 cm^2, and left ventricle/body surface mass = 115 g/m^2. A cardiac surgery was scheduled for valve replacement. Computer tomography of the thorax showed aortic valve calcification.

Case 3: R.C., 53 years old, male, hypertension, Wilms' tumor was detected when he was 1 year and 9 months old. He underwent right nephrectomy. Radiotherapy in the mediastinum due to metastasis.

In 2006, Doppler echocardiogram showed tricuspid aortic valve with calcification, moderate stenosis, mean gradient = 34 mmHg, and mild aortic reflux. Simpson ejection fraction (EF) = 70%. Left ventricle/body surface mass = 115 g/m^2.

In 2009, when he was 50 years old, the patient reported mild retrosternal pain and sought for medical assistance. He underwent cardiac catheterization with stent implant in the right coronary artery due to 90% distal stenosis. Doppler echocardiogram was performed and showed severe aortic stenosis, mean gradient = 52 mmHg, VA = 0.8 cm^2, mild reflux and left ventricular/body surface mass = 98 g/m^2. Currently, the patient is in functional class I. Thorax CP showed aortic valve calcification, ascending aorta calcification, and pulmonary aorta trunk calcification (Figure 2).

Case 4: F.G.N., 48 years old, male, diagnosed with lymphoma when he was 22 years old (1986). Underwent chemotherapy and radiotherapy. In 2009, when he was 45 years old, the patient reported tachycardia and sought for medical assistance. Doppler echocardiogram showed thickened aortic valve, calcified tricuspid, severe stenosis (mean gradient = 42 mmHg) and mild reflux. Simpson EF = 52%, left ventricle/body surface mass = 131 g/m^2. Currently, the patient is in functional class I. Computer tomography showed aortic valve calcification and ascending aorta calcification (see Table 1).

Discussion

Most of the information on cardiac complications is based on studies conducted with Hodgkin disease patients or breast cancer patients, who develop symptoms after radiotherapy or during follow up[5]. Mediastinum radiotherapy is associated to 2 to 7 fold increase in the risk of valve lesions, acute myocardial infarction, angina and cardiac failure[6].

A study conducted by Van Rijswijk et al. reported the development of valve lesions in 60% of the patients treated with previous radiotherapy in the mediastinum. Fi-

Table 1: Resumo das características clínicas dos pacientes e dos exames realizados

Pacientes	I	II	III	IV
Tipo de tumor	linfoma de Hodgkin	rabdomiosarcoma de mediastino	tumor de Wilms	linfoma
Idade ao realizar Radioterapia	13 anos	34 anos	1 ano e 9 meses	22 anos
Diagnóstico da LVAR	46 anos	44 anos	47 anos	45 anos
Achados ao 1º ECO	Gd* = 23 mmHg , FE† = 65%	Gd = 9 mmHg, AV‡ 1,6 cm2, massa VE§ 83 g/m2, FE 50%	Gd = 34 mmHg FE=70% IAo// leve, massa VE 115 g/m2	Gd = 42mmHg, FE= 52% IAo leve, massa VE=131g/m2
Achados ao 2º ECO	Gd = 43 mmHg, AV 0,9 cm2 massa do VE = 98 g/m2, FE=60%	Gd = 40 mmHg, AV 0,6 cm2 massa VE = 115 g/m2. FE=47%	Gd = 52mmHg, AV= 0,8cm2 , IAo leve, FE = 76%	
Achados na TC	calcificações parietais da aorta ascendente	calcificações parietais da aorta ascendete e da valva aórtica	calcificação do tronco da artéria pulmonar, aorta ascendente e óstio de CD¶	calcificação parietal da aorta
Lesão coronariana	estenose óstio de CD 75%	lesão de TCE# distal 90%, DA** e CD ocluídas	lesão ostial de CD 90%	

brosis and calcifications are the typical changes noted at the echocardiogram, with frequent evolution to cardiac failure and death[6]. The younger the patient is subjected to radiotherapy, the higher is the probability of developing valve lesion over the years. Associated risk factors: high doses of radiotherapy, little cardiac blocking protection and concomitant use of cardiotoxic drugs.

The physiopathogenesis of the valve lesion is based on endothelial dysfunction caused by an active cell process involving chronic inflammation and resulting in decreased flow mediated by vasodilatation of the arteries in the irradiation field. This dysfunction especially compromises endothelial nitric oxide synthesis, production of growth factors and fibrosis, leading to the accumulation of free radicals and direct lesion to the cell DNA. Radiotherapy also has a direct effect on the valves, leading to thickening and fibrosis, retraction and calcification[7].

In a Heidenreich et al.[3] study, 294 patients had undergone previous radiotherapy for Hodgkin lymphoma treatment with high doses of radiotherapy of at least 35 Gy. They observed aortic valve abnormalities are more common than mitral or tricuspid valve abnormalities as a result of the proximity to the radiation field in relation to the other valves mentioned. Most of the patients in this study that had valve structural changes were asymptomatic. Findings obtained after echocardiogram. Patients who had received radiation 10 years ago had prevalence of less significant valve thickening than those irradiated 20 years ago. When adjusted to age and gender, the risks of aortic stenosis increased every 10 years after treatment. This study had a follow-up period of 3.2 + 1.3 years.

More sensible techniques, such as cardiac computer tomography and magnetic resonance, can improve detection effectiveness not only of valve lesions, but also of coronary ostium lesions, especially of the anterior descending artery (ADA) and right coronary artery (RCA) due to its proximity to the radiation field, calcification of the aorta, thickening and pericardial calcification[1,5].

The advancement of radiotherapy techniques allowed for decreased dose on coronary arteries over the decades[8]. However, the inclusion of chemotherapy schemes with anthracyclines and the use of trastuzumab turn the analysis of heart and coronary arteries spread dose increasingly important.

The traditional technique includes two tangent fields that cover the breast parenchyma, skin, and subjacent thoracic wall. However, as it is not a modulated beam, the dose is spread over the pulmonary tissues below the thoracic wall and heart (especially left anterior descending coronary artery and ventricles) in cases of left breast radiotherapy.

The advancement beam intensity modulated radiation allows for a considerable reduction of the dose that

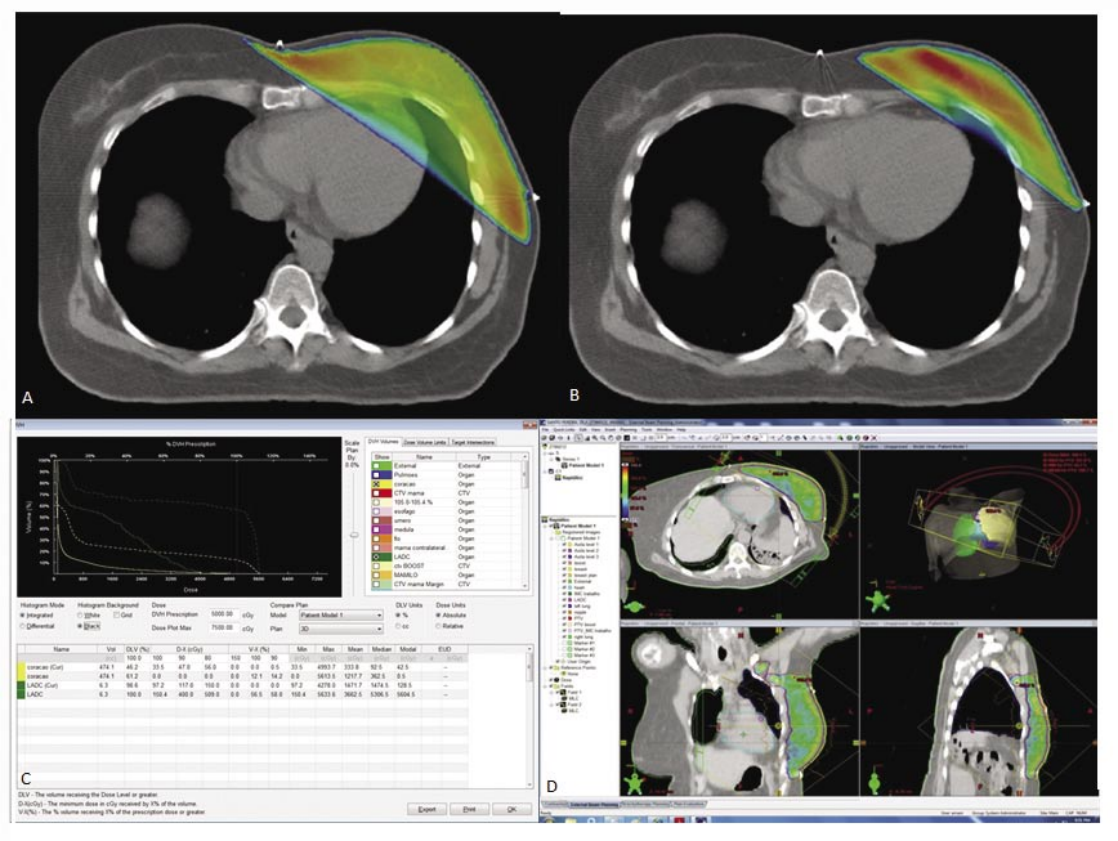

Image A: : Dose distribution on external left breast radiotherapy planning with conformational radiotherapy.

Image B: Dose distribution over the left breast by the h-DAO (IMRT) technique. Images granted by Clínicas Oncológicas Integradas captured on April 16th, 2012, Prowess software.

Image C: Dose volume histogram showing a decreased dose over the anterior descending coronary artery and over the heart with the h-DAO technique compared to the conformational technique. Images granted by Clínicas Oncológicas Integradas captured on April 16th, 2012, Prowess software.

Image D: Left breast radiotherapy planning with VMAT. Images granted by Clínicas Oncológicas Integradas captured on May 21st, 2012, Eclipse planning software. Images granted by Clínicas Oncológicas Integradas captured on May 21st, 2012, Eclipse planning software

Figure 3: Breast radiotherapy: Comparison between conformational planning and beam intensity modulated technique.

is spread over the heart, which will probably result in a decreased mortality rate due to cardiac events.

Intensity Modulated Radiotherapy (IMRT) modulates the radiation beam through computer calculated algorithms. This allows the dose to be concentrated in the target volume, and a significant dose reduction in surrounding normal tissues is seen. Additionally, this technique offers more homogeneous dose coverage over the target, decreasing hot spots (spots with dose higher than the dose prescribed).

Innumerous studies in the literature showed IMRT is capable of reducing the spread dose over the skin, lungs, heart and coronary arteries, leading to a lower incidence of skin and cardiac toxicity in 15 years[9,10].

However, radiotherapy is in constantly development and, nowadays, a new technique, considered to be the evolution of IMRT, is being used. This new technique modulates the beam through radiation fields in the form of arcs (VMAT – Volumetric Modulated Arch Therapy). Although there are few studies on VMAT applied to breast cancer, it is possible to note a dose reduction over the heart, skin and lung when compared to the conventional and IMRT[11] techniques (Figure 3).

The management of asymptomatic patients with valve disease is still not clear. Studies present a trend to initiate follow-up with echocardiography after 10 years of irradiation due to the high prevalence of this lesion in this patients[3].

However, new studies are necessary with a larger number of patients using the current therapy, in whi-

ch the radiotherapy dose is lower than the one seen in previous studies (20 to 30 Gy), with cardiac block protection to assess the actual prevalence of asymptomatic patients with valve disease, the progression rate of asymptomatic patients and if detection with early treatment brings benefits to patients.

In these four cases, Doppler echocardiogram showed involvement of the mitral aortic curtain, calcification of the aortic valve and ascending aorta. And it is important to highlight the evolution aspect of valve lesion. CT was useful to complement the diagnosis considering other findings, as coronary lesion and calcification of the pulmonary artery trunk.

The First Brazilian Guideline for Cardio-Oncology4 emphasizes the cooperation between cardiologists and oncologists to early identify cardiovascular complications in oncology patients. The performance of Doppler echocardiogram to detect and follow valve abnormalities is fundamental. Due to disease progression over time, and according to data obtained in the literature, it is recommended to perform echocardiogram 10 years after radiotherapy[12], and follow-up must be done throughout life.

References

1. Carlson RG, Mayfield WB, Normann S, Alexander JA. Radiation – associated valvular disease. Chest. 1991;**99**(3);538-45.
2. Veinot JP, Edwards WD. Pathology of radiation-induced heart desease:a surgical and autopsy study of 27 cases. Hum Pathol. 1996;**27**(8):766-73.
3. Heindenreich PA, Hancock Sl, Lee Bk, Mariscal CS, Schinttger I. Asymptomatic cardiac disease following mediastinal irradiation. J Am Coll Cardiol. 2003;**42**(3):743-9.
4. Kalil Filho R, Hajjar LA, Bacal F, Hoff PM, Diz M del P, Galas FRGB, et al. I Diretriz Brasileira de Cardio-Oncologia da Sociedade Brasileira de Cardiologia. Arq Bras Cardiol. 2011; **96**(2supl.1): 1-52.
5. Benjmin F, Byrd III, Lisa A.Cardiac complications of mediastinal radiotherapy. J.Am Coll Cardiol.2003;**42**(4):750-1.
6. van Rijswijk S, Huijeregts MA, Lust E,Strack van J, Schijndel R,. Mini –review on cardiac complications after mediastinal irradiation for Hodgkin lymphoma.Neth J Med. 2008; **66**(6):234-7.
7. Wethal T, Lund MB, Edvardsen T, Fossa SD, Pripp AH, Holte H, et al. Valvular dysfunction and left ventricular changes in Hodgkin's lymphoma survivors: a longitudinal study. Br J Cancer. 2009; **101**(4):575-81.
8. Darby SC, McGale P, Taylor CW, Peto R . Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. Lancet Oncol. 2005; **6**(8):557-65.
9. Pignol JP, Olivotto I, Rakovitch E, Gardner S, Sixel K, Beckham W, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. J Clin Oncol. 2008;**26**(13):2085-92.
10. Dogan N, Cuttino L, Lloyd R, Bump EA, Arthur DW. Optimized dose coverage of regional lymph nodes in breast cancer: the role of intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys. 2007;**68**(4):1238-50.
11. Popescu CC, Olivotto IA, Beckham WA, Ansbacher W, Zavgorodni S, Shaffer R,et al.Volumetric modulated arc therapy improves dosimetry and reduces treatment time compared to conventional intensity-modulated radiotherapy for locoregional radiotherapy of left-sided breast cancer and internal mammary nodes. Int J Radiat Oncol Biol Phys. 2010;**76**(1):287-95.
12. Galderisi M, Marra F, Esposito R, Lomoriello V, Pardo M, Divitiis O. Cancer therapy and cardiotoxity: the need of serial Doppler echocardiography. Cardiovasc Ultrasound. 2007; **5**(4):1-14.