

Heart Valve Injury Induced by Mediastinum Radiotherapy in Cancer Treatment

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Abstract: Radiotherapy as monotherapy or in combination with chemotherapy, has contributed to the drop in mortality rates related to neoplasms in the last 60 years. However, irradiation may promote heart damage and involvement is very common. As a result, VHD (valvular heart disease) is one of the earliest cardiovascular events post-radiotherapy. What it concerns to valve disease induced by chemotherapeutics, there are still only few studies. However, patients treated with chemotherapy in combination with radiotherapy had twice the risk of developing the disease when compared to those treated by radiotherapy alone. The heart injury caused by radiotherapy begins with damage to the endothelium and results in fibrosis and diffuses calcification primarily of the mitral and aortic valves. The echocardiography is the tool of choice to the patient's assessment and follow-up after exposure. Prevention is the best option to face the valve damage induced by radiation.

Key words: Radiation induced valvular disease, radiation cardiotoxicity, chemotherapy cardiotoxicity, cancer related valvular disease.

1. Introduction

Cancer is the second most cause of death worldwide, accounting for 8.8 millions of deaths in 2015. Overall, 1 in each 6 deaths has cancer as its cause, and approximately 70% of cancer deaths occur in low and middle income countries. About one third of these deaths occur due to the adoption of an unhealthy lifestyle such as obesity, low fruit and vegetable intake, sedentary lifestyle, smoking and excessive consumption of alcohol. Although the dietary and behavioral causes are preventable, the number of new

cases is expected to raise about 70% in the next two decades [1].

Radiotherapy as a monotherapy or in combination with chemotherapy, has contributed to the drop in mortality rates related to neoplasms in the last 60 years. From 1940 onwards, it began to be used in HL (Hodgkin's lymphoma) management, increasing the survival rate in 60% of cases, and in many of them the therapy is used with curative intent. In addition, it also promotes recurrence reductions and survival increases for those who suffer from breast cancer. This therapeutic approach, besides being beneficial for patients in those two aspects, helps in the treatment of other types of tumors. However, the irradiation in this anatomical portion may promote heart damage. HL and

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breast cancer survivors are more likely to evolve with fatal cardiovascular events. In patients with HL, the exposure of cardiac valves to radiotherapy may significantly increase the risk of having VHD (valvular heart disease) as the first cardiovascular event after the treatment, especially in 30 Gy doses [2, 3]. Other neoplasms installed near the heart, such as the esophagus and lung, are capable of promoting cardiac damage, but HL and breast cancer are the main culprits [3, 4].

High tech tools for diagnostic accuracy and the new therapeutic options, allowed life expectancy of those affected by neoplastic diseases to proportionately increase [2]. As a result of this new outlook, after decades of tumor remission, we have witnessed in the long term, sequelae from radiotherapy and chemotherapy exposure that can promote cardiac damage [2, 3]. Left ventricular dysfunction is a well-known adverse event of tetracycline administration, but loss of systolic function is not the only late consequence. Many popular chemotherapeutic agents may be toxic to the myocardium and cause cardiac dysfunction such as doxorubicin, a widely used anthracycline. However, the chemotherapy role in valvular diseases is poorly studied [5]. Although chemotherapy drugs do not directly affect cardiac valves, VHD may be observed often in cancer patients. This association can be explained by the existence of previous valvular injuries, exposure to radiotherapy, previous history of infective endocarditis and secondary left ventricular dysfunction [3, 6]. In addition, genetic factors seem to increase the probability of cardiotoxic side effects [7].

The valve involvement in cancer treatment is very common in radio-induced cardiac lesions. [2, 4]. Despite being a late effect, diagnosed by accident or after the beginning of the symptoms, the VHD induced by radiation exposure is an usual report in cancer treatments that require mediastinal irradiation, affecting around 10% of exposed patients and reaching up to 80% in a historical series of autopsies [2, 3, 7].

It accounts for the fibrosis and calcification of the aortic root, cusps of the aortic valve, mitral valve annulus and the basal and medial portions of the mitral valve leaflets. However, mitral valves extremities and commissures are spared, allowing distinction from rheumatic disease [4, 6].

2. Objectives

The objective is to elucidate the etiology, diagnosis and management of valve damage as a late result of radiotherapy in patients undergoing oncological treatment.

3. Materials and Methods

This paper is a systematic review developed from pertinent evidence retrieved by a selective research in PubMed and other databases, during the time between October of 2017 and March of 2018. Keywords chosen as searching tools were “radiation induced valvular disease”, “radiation cardiotoxicity”, “chemotherapy cardiotoxicity” and “cancer related valvular disease”. Among the articles found, 24 regarding Heart Valve Injury Induced by Cancer Treatment were considered eligible, respecting the inclusion and exclusion criteria. The guidelines from European Society of Cardiology and the European Society of Medical Oncology were continuous source for this article.

4. Results

The difficulty in measuring the incidence of valvar cardiotoxicity induced by mediastinal irradiation is related to the interval between the radiotherapy exposure and the clinical manifestation of the cardiac disease, besides being potentiated when there is concomitant use of cardiotoxic chemotherapeutic agents and previous history of cardiovascular disease [2, 8]. Scientific evidence of valvar disease as late result of radiation was scarce, generating doubts. However, since 1900 and 2000, we have identified an increase in reports, mainly from the analysis of individuals affected by HL and breast cancer who

received thoracic radiotherapy [5, 8]. Studies have not only confirmed this association, but also listed the risk factors. Table 1 demonstrates the main risk factors that influence the incidence and severity of heart disease, the higher the radiation dose and body volume exposed, the lower the age at the time of exposure, the longer the time since the end of treatment, the use of adjuvant chemotherapy, the type of radiation source, and metabolic risks factors such as hypertension, smoking, obesity, diabetes mellitus, in addition to previous cardiovascular diseases [5, 7]. It is known that radiation induced cardiovascular diseases are recognized as the main cause of non-malignant death in these patients, accounting for one fourth to one third of their mortality [8].

Nowadays, modern machines and techniques that offer increased cardiac protection may lower the risk of cardiotoxicity after thoracic radiation, reducing the occurrence of VHD as a late adverse event of cancer treatment. However patients with HL or breast cancer, who were treated in the past with methods, now considered obsolete [7, 9], may still evolve with hemodynamic repercussions. After receiving radiation doses between 30 and 42 Gy, and a 11.2-year average follow-up, patients with HL have twice the relative risk of developing heart disease. Patients with cancer in the

left breast that underwent chemotherapy with cardio toxic potential and radiotherapy have an even greater risk of cardio toxicity, suggesting a synergic therapeutic effect on cardiac structure [7, 10]. Schellong et al. indicate that currently in pediatric oncology, radiation doses have already been massively reduced. A study with 1,132 children with HL and a 15-year average follow-up, showed that heart disease can be detected in 4.4% of cases and in two thirds of these cases, the cardiac valve damage was the diagnosed abnormality. However, we estimate that the future risk for patients who are undergoing treatment now may be considerably lower [10]. A recent cohort study with 82 HL survivors treated with mediastinal radiotherapy, proved through echocardiography that valvar disease was more prevalent in irradiated patients and increased with time since treatment. In addition, after 20 years of irradiation, the majority of HL survivors developed clinically important valve disease. Aortic regurgitation did not occur within 10 years after treatment in patients less than 40 years of age [11].

As it can be seen in Fig. 1 below, the heart injury caused by radiotherapy begins in the microvasculature, few minutes after the start of the procedure, damaging the endothelium and making it more permeable. Endothelial cell chemotactic activity is increased, attracting

Table 1 Risk factors associated with radiation induced VHD.

High radiation dose
Body volume exposed
Adjuvant chemotherapy
Type of radiation source
Cardiovascular and metabolic risks factors
Previous cardiovascular diseases

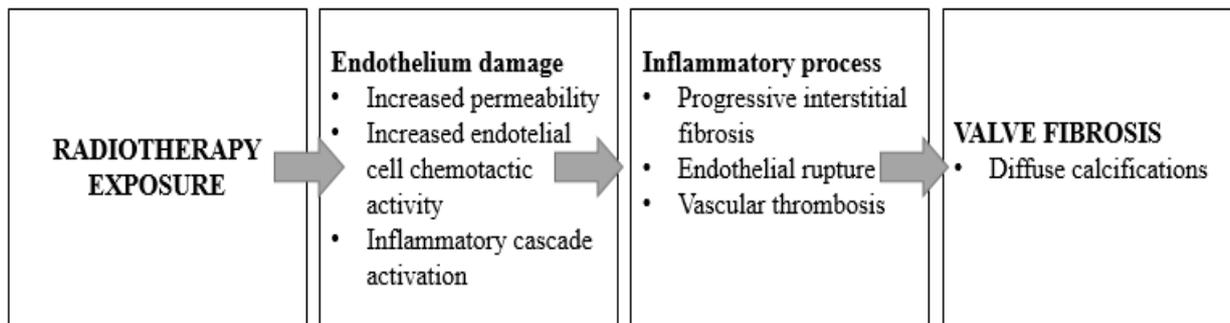


Fig. 1 Process of valvular heart injury by radiotherapy exposure.

neutrophils and starting the inflammatory cascade [12], directly involved in the myofibroblasts regulation and in the synthesis of collagen [13, 14]. The final result is a progressive interstitial fibrosis, endothelial rupture and vascular thrombosis that can generate valve fibrosis and diffuse calcification. Fibrosis and pericardial constriction are important and frequent consequences of radiotherapy exposure. However, the injuries volume and distribution vary [2, 5, 8]. Many times, calcifications are relevant, being observed in the left fibrous trigone and reaching the septum in VHD [15]. Certainly, fibrosis is the main process in which damage from chronic radiation occurs; being that the first valve alteration appears to be the formation of valvular retractions, and then, valve insufficiency. Both of them preferably involve mitral and aortic valves, occurring in the first 10 years after radiotherapy. Progression to fibrotic thickening and calcification of the valves occurs much later, appearing 20 years after radiotherapy [8].

Most non-coronary heart diseases associated to radiation are valve diseases, being that besides VHD, other adverse events may be induced, like pericarditis, abnormalities in electrical conduction, accelerated atherosclerosis, myocardial systolic and diastolic dysfunction, coronary artery disease, difficulty in healing of myocardial and pericardial wounds, turning heart surgery even more challenging [8, 11, 14]. Patients exposed only to radiotherapy are more likely to present diastolic dysfunction, differing from those exposed to radiotherapy combined with administration of anthracyclines, these tend to evolve with systolic dysfunction [7, 9, 16]. The systolic dysfunction is the last event to occur in the cascade and should be considered a sign of chronic disease [8].

Acute cardiotoxicities such as cardiac arrhythmia during anthracycline infusions must be separated from

chronic cardiotoxicities such as restricted left ventricular pump functions and VHD. Cardiac toxicity caused by paclitaxel takes the form of sub-acute or acute bradycardia, heart block and atrial or ventricular arrhythmias. Cardiac symptoms in the treatment with 5-fluorouracil generally occur during the initial hours following the start of therapy. The most frequent symptom is reversible, typical angina pectoris, but myocardial infarctions have also been described [7].

Radiation doses and the time when the patient was treated, have an impact on the natural history of VHD, such as it is demonstrated in Table 2. Patients who were irradiated under obsolete protocols between 1965 and 1995 had their risk of having VHD increased by 7. Patients treated in the last few decades will continue to experience higher rates of VHD in the next decades [8]. CMR (cardiac magnetic resonance imaging) in 20-year survivors of mediastinal irradiation, at a median dose of 40 Gy, detected hemodynamically relevant valve damage in 42% of cases, perfusion deficits in 68%, and evidence of prior infarctions in 29% [7, 17], showing hemodynamic dysfunction of cardiac structures. However, there was no evidence of direct relationship between the radiation dose and specific abnormal findings [18]. Radiation dose and heart injury does not directly relate to each other, as exposure is related to the patients profile and with previous risk factors. However, we do know that doses around 40 Gy are capable of harming cardiac valves, 35 Gy doses interfere in the normal pericardic and myocardic physiology, and 30 Gy in the coronary arteries. Besides, in combinations including anthracyclines, the critical dose thresholds are lower [19].

Chemotherapy versus Radiotherapy: What it concerns to valve disease induced by chemotherapeutics, there are still only few studies in this research line. However, we do know that patients

Table 2 Radiation dose versus heart injury.

30 Gy radiation dose	Interfere in coronary arteries
35 Gy radiation dose	Interfere in pericardic and myocardic physiology
40 Gy radiation dose	Harming cardiac valves

treated with radiotherapy combined with chemotherapy had twice the risk of those who were treated with radiation alone, being an additive risk and not a multiplicative one. In addition, patients with cardiomyopathy induced by anthracycline are under the risk of mitral insufficiency, although, not related to an intrinsic valve disease (mitral insufficiency could potentially confuse these results) [5]. Treatment with anthracyclines seems to increase the risk of valve damage [15]. A recent study was able to outline the type of valve dysfunction induced by chemotherapeutics, being that the anthracyclines were related to direct toxic effects on the valves, not related to cardiomyopathy or ventricular dilation, once they were co-related more with aortic degeneration than mitral [20].

Nowadays, became well defined that combined therapies have higher cardiotoxicity potential (for example, anthracycline plus trastuzumab or paclitaxel plus anthracyclines). In cardiotoxicity induced by anthracyclines we include as risk factors: age, previous heart injury, radiation in cardiac area, but primarily the cumulative dosage of the drug, that should be used only after clinical examination, including electrocardiogram and echocardiography with measurement of the left ventricular ejection fraction. In contrast with myocardial injury induced by anthracycline, myocardial injury induced by trastuzumab seems to be reversible, not having an increase in risk after the end of the treatment [7].

Diagnosis: Clinically, valvar and mitral insufficiencies are the most common VHDs and when stenosis occurs, the aortic valve is more frequently afflicted. In a large meta-analysis, left side valves were more commonly affected, accounting for 92% of valve involvement. These findings were possibly caused by increased left ventricular pressure exacerbating valve damage on that side [5, 8, 21].

Due to its accessibility and versatility, the echocardiography is the chosen method of serial evaluation. In addition its three-dimensional modality

demonstrates importance mainly for evaluation of the mitral commissures. The imaging exam must be realized before and after radiotherapy for VHD diagnosis and follow-up [5-7, 22]. Supported by the recent literature, the use of transthoracic echocardiogram is the screening tool of choice to evaluate baseline left ventricular baseline ejection fraction, diastolic function and VHD. Echocardiography is also important in the assessment of restrictive cardiomyopathy and constrictive pericarditis [8, 22]. Therapy-related cardiac dysfunction is defined as a decrease between 10% and 53% in left ventricular ejection fraction, according to 2D echocardiography measurements [22].

When suspecting of VHD due to the clinical finding of a new heart murmur, transthoracic Doppler echocardiography is the recommended first-line imaging, reserving the transoesophageal echocardiography when the initial evaluation is non-diagnostic [23]. Based on the usual clinical scenario, there are many asymptomatic patients, being that imaging studies may be the first to indicate valve disease [21]. Although radiation-induced injuries exhibit many unique features such as uniform valvular thickening from fibrosis, greater involvement of left sided valves, thickening of the aortic mitral curtain, regurgitation prior to stenosis and preservation of commissural fissures, diagnostic criteria are not different from those used to indicate traditional degenerative valvular pathology [5].

CMR became a reference standard to the volumetric measurements of the cardiac chamber size and ventricular function. The advantages of CMR include highly accurate and reproducible measurements of left ventricular ejection fraction, ability to measure myocardial deformation (strain assessment), valvular regurgitation evaluation and detection of myocardial scarring by delayed gadolinium enhancement. Although the American College of Cardiology and the American Heart Association Guidelines identify CMR as a valid imaging study for the cardiotoxicity

screening, most centers do not use it as the primary screening imaging study [22]. Resonance imaging offers many advantages over echocardiography and is considered more accurate and reproducible in many clinical situations, such as assessment of patients with valve insufficiency or to demonstrate the severity of stenosis using kinetic phase contrast techniques [21]. However, it is seen as a second line modality in the evaluation of cardiotoxicity, due to the availability of specialists, the higher cost and the duration of the examination, which limits its wide clinical utility [22].

CMR and CT (computed tomography) may be used to assess the severity of VHD, but cardiac CT is mainly useful for detecting extensive calcifications of the ascending aorta, which may lead to a higher operative risk and sometimes prohibit conventional cardiovascular surgery. Transcatheter valve implantation may be a suitable option in this situation. It has been shown that CT imaging may be of greater use in the detection of heart disease in cancer survivors in their second or third decade post radiotherapy [2, 8]. Although no gold standard was applied, the measurement of abnormal longitudinal strain on the echocardiography was correlated with reduced quality of life and lower mean 6-min walk distances, even when it was the sole abnormal finding. Thus, while the reduced ejection fraction is a late detection, abnormal deformation measurements may announce early-onset disease and are increasingly incorporated into the screening protocols [8].

Several non-invasive cardiac imaging techniques are available for the early screening, detection and follow-up of patients at high risk for cardiotoxicity [22]. As in patients receiving anthracycline, in which the aim of the image is to detect subclinical decline in left ventricular function, when such a decline occurs, the chemotherapy regimen is adjusted to limit cardiotoxicity [21]. However, greater multidisciplinary collaboration between specialists in cardiology, oncology and radiology is needed in order to formulate guidelines that seek to optimize and standardize

surveillance regimes in cancer patients. The optimal long-term screening approach for cancer survivors has not yet been elucidated [22].

Prevention: The prevention of this result is the main way to deal with radiation-induced valvular damage. In addition, cardiovascular morbidity and mortality of radiotherapy can be prevented primarily with dose reduction and radioprotection. As a form of secondary prevention, there is the screening and reduction of damages or the modification of risks [5, 8]. No pharmaceutical product is currently approved by the FDA (Food and Drug Administration) in this regard [8].

Approaches with the use of antioxidants have been object of study, however its use is controversial for not having demonstrated effect. Dexrazoxane, an intracellular iron chelator, is discussed as an option in anthracycline-induced cardiomyopathies [7, 8].

Consistently, it can be said that the main form of prevention is the reduction of exposure to radiation, with practices such as: exclusion of the largest possible part of the myocardium from the treatment field, using breast plates or performing deep inspiration and inspiratory block. In this same intention, a major advance is the use of intensity-modulated radiotherapy, modality in which the radiation beams fit the tumoral form. All of these techniques require imaging technologies and superior software that provide radiation more accurately, often up to millimeters of the desired target, and with margins much smaller than those used in the previous century. The most recent technology to be developed is that of proton radiotherapy, a mode in which the delivery of particles is through protons as opposed to photons. The advantage to this technique is that the majority of energy is delivered at a specific narrow tissue depth with minimal entry and zero exit absorption [5, 8].

The European Cardiovascular Imaging Association and the American Society of Echocardiography in 2013 recommended aggressive modification of risk factors and annual medical visits. They also

recommended baseline echocardiography before radiotherapy, followed by echocardiography 10 years after treatment and then every five years in patients without heart disease. For patients with one or more conventional risk factors, screening echocardiography was recommended in the fifth year after treatment and the noninvasive stress test was recommended 5-10 years after treatment as well as at 5-year intervals with stress echocardiography in these patients [23].

Treatment: The main challenge of the treatment is the prevention, as it relies primarily on the strategies that require advanced technologies and superior software. There are no studies showing drugs capable of reversing the course of valvular disease when it is already established. Therefore, at the late stage of disease, we focus on treating the symptoms. Similarly, there are no medications that directly interfere with cardiac remodeling and inflammatory changes from radiation. Thus, the treatment is based on methods of prevention and frequent follow-up to detect cardiac involvement as early as possible. Cardiac treatment should begin with the modification of the conventional risk factors, which are particularly dangerous in this population, demonstrating more than double the relative risk of cardiac events in these patients compared to corresponding patients in the general population. Thus, hypertension, hyperlipidemia and diabetes mellitus should be aggressively administered, as well as lifestyle modifications, such as cessation of smoking, weight loss and exercise. The identification and treatment of hyperlipidemia in cancer survivors with a history of radiotherapy are emphasized, given their direct correlation after radiotherapy and atherosclerosis [7, 8].

Statins have been studied extensively in rodent and *in vitro* human models and were promising. These studies may begin to elucidate the role of early statin therapy in reducing the long-term risk of radio-induced heart disease. ACE (Angiotensin converting enzyme) inhibitors are a commonly prescribed class of drugs with radioprotective potential, although there are no

prospective studies evaluating the efficacy of these drugs in patients undergoing radiation therapy. However, ACE and beta-blockers are important pharmacological treatments, mainly in left ventricular dysfunction, with the goal being to achieve blood pressure lower than 140×90 mmHg and heart rate below 70 bpm, and the maximum tolerated dose can be used. The following agents can also be used: aldosterone antagonists, digitalis glycosides, diuretics and ivabradine [7, 8, 15]. The use of the latter two drugs is an interesting prevention, but it is necessary to prove that the mild prevention provided by the early alteration of the LVEF (left ventricular ejection fraction) has favorable consequences in terms of long-term cardiac events [15].

The treatment of radio-induced VHD is the same as in non-irradiated patients; however, it is often complex, bivalvular lesions, associated with restrictive myocardial damage and important comorbidities, mainly pulmonary [15]. Therefore, surgical indications for radiation-induced or radiation-induced valvular dysfunction do not differ from traditional degenerative valvular pathology. However, patients with severe VHD as a result of cancer treatment should have their perioperative risks carefully considered, with meticulous evaluation of the respiratory status, since in these the mortality is much higher [5, 15]. Studies have shown that TAVI (transcatheter aortic-valve implantation) plays an increasingly important role in the treatment of patients with aortic disease induced by radiation being equal to or superior than replacement of the surgical valve replacement in high-risk patients, given the associated morbidity and mortality in this population [24]. Another option is the use of MitraClip, a technique successfully established in it [5].

5. Conclusions

The inherent risk of radiotherapy combined with agents capable of offering cardiotoxic risks cannot yet be conclusively evaluated due to the need for long follow-up periods of the surviving patients. Therefore,

all efforts must be made in planning the exposure to radiotherapy, in order to reduce the dose received by cardiac structures. The younger the patient is at the time of treatment, the more critical is the need for surveillance, since their relative risk is greater. Continuous improvements in radiation techniques, changes in the profile of the treated population, absence of cardiac disease, previous exposure to radiotherapy, increase the awareness of physicians about the long-term cardiovascular side effects. Despite the advances, the excess risk of morbidity and mortality persists. Therefore, it is imperative that the cardio-oncological treatment be initiated and planned before the start of the RT to establish the base situation for a continuous surveillance throughout the life of the patient. Given that knowledge of the clinical determinants of valve disease in cancer patients is a prerequisite for the development of follow-up and screening programs.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

References

- [1] <http://www.who.int/mediacentre/factsheets/fs297/en/>.
- [2] Zamorano, J. L., Lancellotti, P., Muñoz, D. R., Aboyans, V., Asteggiano, R., Galderisi, M., et al. 2016. "2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines. The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)." *European Heart Journal* 37: 2768–801.
- [3] Plana, J. C., Galderisi, M., Barac, A., Ewer, M. S., Ky, B., Scherrer-Crosbie, M., et al. 2014. "Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging." *Eur. Heart J. Cardiovasc Imaging* 15: 1063–93.
- [4] Hull, M. C., Morris, C. G., Pepine, C. J., and Mendenhall, N. P. 2003. "Valvular Dysfunction and Carotid, Subclavian, and Coronary Artery Disease in Survivors of Hodgkin Lymphoma Treated with Radiation Therapy." *JAMA* 290: 2831–7.
- [5] Stewart, M. H., Eiman Jahangir, E., and Polin, N. M. 2017. "Valvular Heart Disease in Cancer Patients: Etiology, Diagnosis, and Management." *Curr. Treat Options Cardio. Med.* 19: 53.
- [6] Hering, D., Faber, L., and Horstkotte, D. 2003. "Echocardiographic Features of Radiation-Associated Valvular Disease." *Am. J. Cardiol.* 92: 226–30.
- [7] Schlitt, A., Jordan, K., Vordermark, D., Schwamborn, J., Langer, T., and Thomssen, C. 2014. "Cardiotoxicity and Oncological Treatments." *Deutsches Arzteblatt International* 111 (10): 161–8.
- [8] Cuomo, J. R., Sharma, G. K., Conger, P. D., and Weintraub, N. L. 2016. "Novel Concepts in Radiation-Induced Cardiovascular Disease." *World J. Cardiol.* 8 (9): 504–19.
- [9] Adams, M. J., Lipsitz, S. R., Colan, S. D., Tarbell, N. J., Treves, S. T., Diller, L., et al. 2004. "Cardiovascular Status in Long-Term Survivors of Hodgkin's Disease Treated with Chest Radiotherapy." *J. Clin. Oncol.* 22: 3139–48.
- [10] Schellong, G., Riepenhausen, M., Bruch, C., Kotthoff, S., Vogt, J., Bölling, T., et al. 2010. "Late Valvular and Other Cardiac Diseases after Different Doses of Mediastinal Radiotherapy for Hodgkin Disease in Children and Adolescents: Report from the Longitudinal GPOH Follow-up Project of the German-Austrian DAL-HD Studies." *Pediatr Blood Cancer* 55: 1145–52.
- [11] Bijl, J. M., Roos, M. M., van Leeuwen-Segarceanu, E. M., Vos, J. M., Bos, W. W., Biesma, D. H., et al. 2016. "Assessment of Valvular Disorders in Survivors of Hodgkin's Lymphoma Treated by Mediastinal Radiotherapy ± Chemotherapy." *Am. J. Cardiol.* 117: 691–6.
- [12] Yusuf, S. W., Sami, S., and Daher, I. N. 2011. "Radiation-Induced Heart Disease: A Clinical Update." *Cardiol. Res. Pract.* 2011: 317659.
- [13] Fajardo, L. F., and Stewart, J. R. 1973. "Pathogenesis of Radiation Induced Myocardial Fibrosis." *Lab. Investig.* 29 (2): 244–57.
- [14] Fajardo, L. F., and Stewart, J. R. 1971. "Capillary Injury Preceding Radiation-Induced Myocardial Fibrosis." *Radiology* 101 (2): 429–33.
- [15] Marlière, S., Vautrin, E., Saunier, C., Chaikh, A., and Gabelle-Flandin, I. 2016. "Radiation-Related Heart Toxicity: Update in Women." *Ann. Cardiol. Angeiol. (Paris)* 65 (6): 411–9.
- [16] Lenneman, C. G., and Sawyer, D. B. 2016. "Cardio-Oncology: An Update on Cardiotoxicity of Cancer-Related Treatment." *Circ. Res.* 118: 1008–20.
- [17] Machann, W., Beer, M., Breunig, M., Störk, S., Angermann, C., and Seufert, I. 2011. "Cardiac Magnetic Resonance Imaging Findings in 20-Year Survivors of

- Mediastinal Radiotherapy for Hodgkin's Disease." *Int. J. Radiat. Oncol. Biol. Phys.* 79: 1117–23.
- [18] Vordermark, D., Seufert, I., Schwab, F., Kölbl, O., Kung, M., Angermann, C., et al. 2006. "3-D Reconstruction of Anterior Mantle-Field Techniques in Hodgkin's Disease Survivors: Doses to Cardiac Structures." *Radiat Oncol* 1: 10.
- [19] Adams, M. J., Hardenbergh, P. H., Constine, L. S., and Lipshultz, S. E. 2003. "Radiation-Associated Cardiovascular Disease." *Crit. Rev. Oncol. Hematol.* 45: 55-75.
- [20] Murbraech, K., Wethal, T., Smeland, K. B., Holte, H., Loge, J. H., Holte, E., et al. 2016. "Valvular Dysfunction in Lymphoma Survivors Treated with Autologous Stem Cell Transplantation: A National Cross-Sectional Study." *JACC Cardiovasc Imaging* 9 (3): 230–9.
- [21] Walker, C. M., Gladish, G. W., Dicks, D. L., Kicska, G., Mitsumori, L. M., and Reddy, G. P. 2013. "Cardiac Complications of Oncologic Therapy." *Radiographics* 33 (6): 1801-15.
- [22] Garg, V., and Vorobiof, G. 2016. "Echocardiography and Alternative Cardiac Imaging Strategies for Long-Term Cardiotoxicity Surveillance of Cancer Survivors Treated with Chemotherapy and/or Radiation Exposure." *Curr. Oncol. Rep.* 18: 52.
- [23] Lancellotti, P., Nkomo, V. T., Badano, L. P., Bergler-Klein, J., Bogaert, J., Davin, L., Cosyns, B., Coucke, P., Dulgheru, R., and Edvardsen, T. 2013. "Expert Consensus for Multi-Modality Imaging Evaluation of Cardiovascular Complications of Radiotherapy in Adults: A Report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography." *Eur. Heart J. Cardiovasc. Imaging* 14: 721-40.
- [24] Möllmann, H., Bestehorn, K., Bestehorn, M., Papoutsis, K., Fleck, E., Ertl, G., Kuck, K. H., and Hamm, C. 2016. "In-Hospital Outcome of Transcatheter vs. Surgical Aortic Valve Replacement in Patients with Aortic Valve Stenosis: Complete Dataset of Patients Treated in 2013 in Germany." *Clin. Res. Cardiol.* 105: 553-9.