Case Report

Between Scylla and Charybdis: Long-Term Cardiovascular Complications After Radiotherapy for Hodgkin's Lymphoma

Ruxandra Jurcut, Oana Savu, Sorin Giusca, Dan Deleanu, Radu Ciudin, Carmen Ginghina

Department of Cardiology, Institute of Emergency for Cardiovascular Diseases "Prof. Dr. C.C.Iliescu" Bucharest, Romania

Key words:
Radiotherapy, left main coronary disease, mammary artery graft, atrioventricular block.

Radiotherapy, an established treatment for local and regional control in neoplastic disease, may have several acute, subacute and chronic side effects. One of the main concerns about mediastinal radiotherapy is the occurrence of long-term cardiovascular complications after oncological treatment. This is an important issue—especially for thoracic neoplasms with long-term survival, such as breast cancer or Hodgkin's lymphoma—because of the increased cardiovascular morbidity and mortality. We present the case of a 50-year-old woman who developed several cardiovascular complications of radiotherapy more than 10 years after the successful treatment of Hodgkin's lymphoma, underlining the particular problems related to optimal therapeutic options in this population.

Manuscript received:
August 23, 2009;
Accepted:
September 28, 2009.

Address:
Ruxandra Jurcut

Department of Cardiology
Institute of Emergency for Cardiovascular Diseases
"Prof. Dr. C.C.Iliescu"
Sos.Fundeni no 258
022328 Bucharest,
Romania
e-mail:
rjurcut@gmail.com

Radiotherapy, an established therapy for local and regional control in neoplastic disease, may have several acute, subacute and chronic side effects. One of the main concerns about mediastinal radiotherapy is the occurrence of cardiovascular side effects a long time after the treatment, the so-called "radiation-induced heart disease".[1] This is an important issue—especially for thoracic neoplasms with long-term survival, such as breast cancer or Hodgkin's lymphoma—because of the increase in cardiovascular morbidity and mortality.

We present a case with cardiovascular involvement long after the successful treatment of a neoplasm, with particular problems related to the optimal therapeutic option.

Case presentation

A 50-year-old female patient was admitted for chest pain on low-grade exertion and cold exposure that started approximately one week before hospital presentation. The patient had a long medical history, starting in 1994 with a stage II B Hodgkin's lymphoma, nodular sclerosis type with mediastinal involvement. At that time, chemotherapy and radiotherapy with a mantle thoracic field were initiated, with a favorable oncological result, remission of oncological disease being maintained until the present.

Ten years after the cancer treatment, in 2004, the patient, then aged 45, started presenting anginal chest pain with progressive worsening. Coronary angiography showed severe left main artery ostial stenosis, without any other coronary artery involvement. Under the circumstances, coronary artery bypass surgery was performed, using two arterial grafts, the left and right internal mammary arteries (IMA). The arteries were skeletonized *in situ* and a "Y" anastomosis was performed: the left IMA was used for grafting the *ramus intermedius* and the right IMA (proximally anastomosed to the left IMA) for the left anterior descending coro-

nary artery (LAD). After surgery, the patient was paucisymptomatic for 4 years.

In 2008 the patient had 5 episodes of syncope, without prodroma; a complete medical evaluation after the first two episodes (ECG, echocardiography, Holter ECG monitoring, tilt test, electroencephalogram, carotid artery ultrasound) failed to show any cause of the syncope. After the evaluation, the patient had another three episodes of loss of consciousness. During the last one the mechanism was elucidated, as the ECG showed transient complete atrioventricular block (Figure 1), and a DDDR pacemaker was implanted. No transitory etiology of the intermittent atrioventricular conduction abnormality was found (normal lab values for blood electrolytes and renal function, no medication with negative chronotropic effect), the possible mechanisms taken into account being either an ischemic substrate or the long term side effect of thoracic radiotherapy.

At the present admission, the patient presented with unstable angina (new onset on low-grade exertion or cold exposure), which made a coronary angiographic reevaluation advisable given the previous coronary revascularization surgery. The patient had no classical cardiovascular risk factors (50-year-old pre-menopausal female, non-smoker, no arterial hypertension or dyslipidemia, no family history of cardiovascular disorders). The physical examination and laboratory data were within normal limits. The ECG showed sinus rhythm and paced QRS complexes. The echocardiographic examination showed normal left ventricular function, without wall motion abnormalities except for pacing-induced septal dyssynchrony, and mild mitral and aortic regurgitation.

Coronary angiography (Figure 2) confirmed the previously diagnosed 70-80% left main coronary artery ostial stenosis, but also found new coronary lesions, in both the native vessels (75% LAD stenosis in segment 2-3, *ramus intermedius* subocclusion) and the grafts (occluded left IMA [*ramus intermedius* bypass], patent right IMA [LAD bypass], with 70% stenosis at the level of the distal anastomosis).

Percutaneous coronary revascularization was performed, including protected angioplasty of the left main coronary artery using a drug-eluting stent, and balloon angioplasty of the distal anastomosis of the LAD graft, with good final results (Figure 3). The patient remained symptom free for 8 months after revascularization.

Discussion

The development of modern anticancer therapies explains why, in a significant proportion of patients, can-

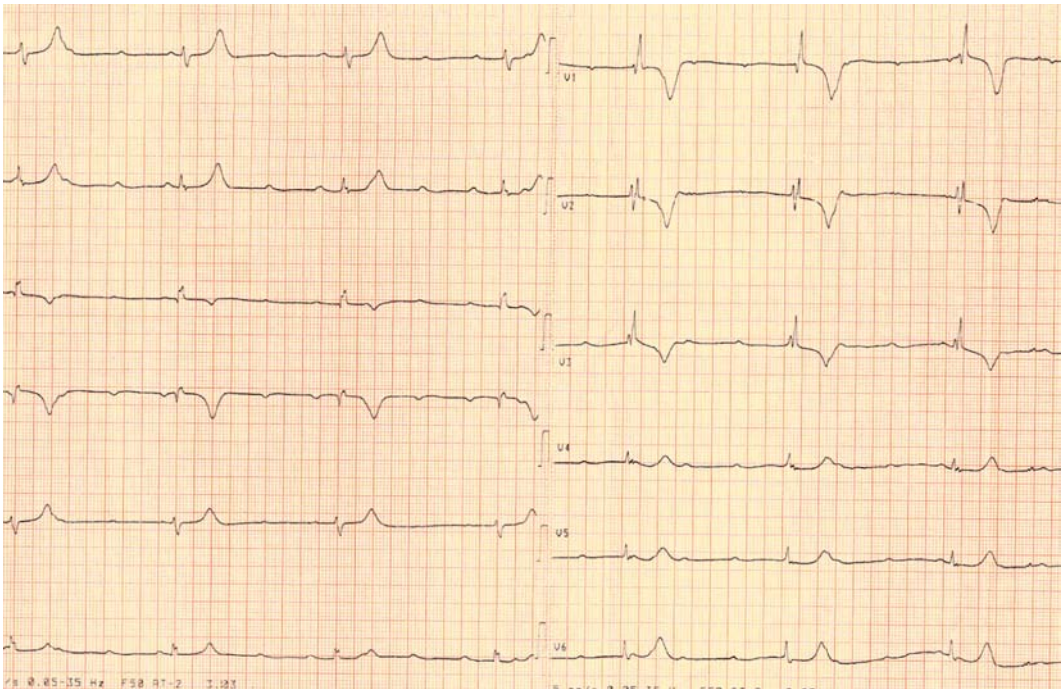

Figure 1. Electrocardiogram: complete atrioventricular block, ventricular frequency 33/min, QRS duration 0.12 s with a right bundle branch block morphology and ST-T secondary changes, atrial sinus rhythm with an atrial frequency ~100/min.

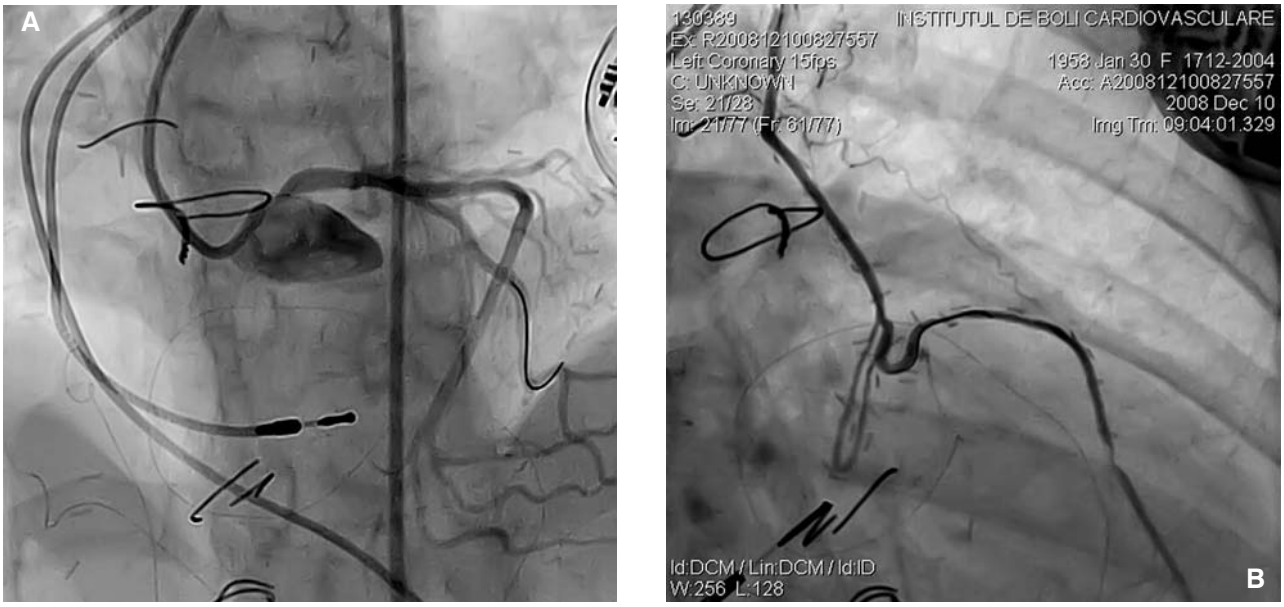

Figure 2. Coronary angiography at presentation. A: 70-80% left main coronary artery ostial stenosis. B: patent right internal mammary – left anterior descending artery bypass, with 70% stenosis at the level of the distal anastomosis.

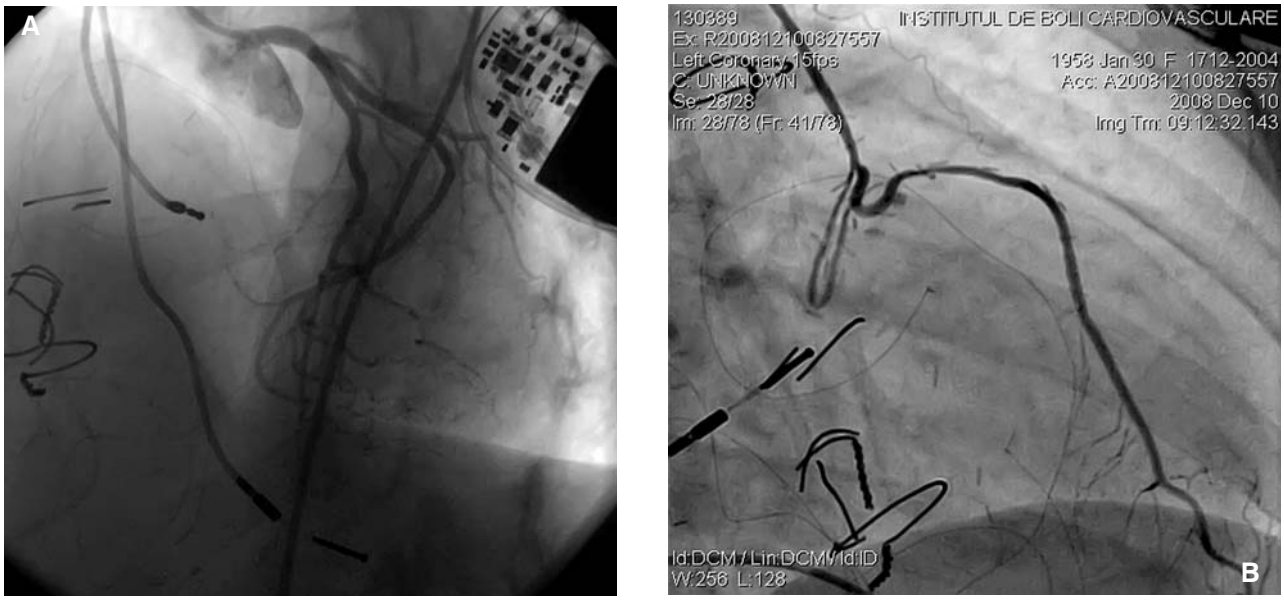

Figure 3. Coronary angiography after percutaneous revascularization. A. Left main coronary artery patency after drug-eluting stent implantation. B. Patent distal anastomosis of the right internal mammary – left anterior descending graft.

cer is now considered as a treatable disease. However, because more and more oncological patients have a long life expectancy, treatment-related comorbidities become one of the essential issues for cancer survivors.

Thoracic radiotherapy, a well-established part of the combined cancer therapy for breast cancer or mediastinal lymphoma, with an important role in local control of the disease, may induce a wide spectrum of long-term cardiovascular disorders, as summarized in Table 1.[2,3] While during the first half of the 20th century the heart was considered a relatively radio-resistant organ,[4] starting in the 1960s several isolated case reports of cardiovascular involvement emerged, with pericarditis, valvular heart disease, conduction abnormalities, and coronary heart disease, and in the 1980s the first studies of large groups of patients were pub-

Table 1. Cardiac complications after thoracic field radiotherapy (modified after refs. 5,6,9,10).

Localization	Type of complication	Time interval from radiotherapy
Pericardial disease	Acute effusion Chronic effusion	During radiotherapy (acute pericarditis)
	Constrictive pericarditis	5-10 years (chronic/constrictive pericarditis)
Myocardial fibrosis	Myocardial fibrosis secondary to microvascular alterations Progressive, restrictive cardiomyopathy with fibrosis may occur Isolated diastolic dysfunction Systolic dysfunction in later stages (more common in patients with concurrent anthracycline chemotherapy)	Subclinical changes in systolic and diastolic cardiac function from 1-6 months after radiotherapy
Coronary artery disease	Structural changes in coronary arteries associated with radiotherapy similar to atherosclerosis Premature fibrosis may accelerate atherosclerosis High frequency of proximal/ostial stenosis High rates of silent ischemia (due to autonomic dysfunction with decreased perception of anginal pain) Increased risk with other coronary risk factors association	>10 years
Valvular disease	Predominantly mitral valve and aortic valve (both regurgitation and stenosis possible)	Prevalence increases with time since therapy
Conduction system/ arrhythmia	Complete or incomplete bundle branch block (right side more frequent) Complete atrioventricular block Persistent tachycardia at a fixed rate and loss of circadian variability in heart rate (due to autonomic dysfunction)	10-15 years

lished. In a large meta-analysis, increased cardiac mortality after radiotherapy was demonstrated after thoracic field radiotherapy in breast cancer and Hodgkin's lymphoma, and vascular complications were also cited in head, neck and testicular cancers.[5] The degree of cardiac involvement correlates with the dosage and cardiac volume included in the radiotherapy field, as well as with time from radiotherapy and younger age during oncological treatment.[6]

The cardiac side effect remains the accelerated coronary artery atherosclerosis, responsible for the doubling of the relative risk of cardiovascular death at 10 years after radiotherapy in patients with breast cancer or Hodgkin's disease.[7] King et al found a 2.8 fold increased risk for fatal myocardial infarction after mantle irradiation for Hodgkin's lymphoma,[8] while Hancock et al showed that mediastinal irradiation in children and adolescents with Hodgkin's lymphoma increases cardiac mortality even in the first 5 years after irradiation.[9]

The mechanisms of radiotherapy-induced myocardial and vascular injury have not been completely understood. Radiotherapy determines endothelial injury and perivascular fibrosis, with subsequent intimal thickening, smooth muscle cell proliferation and collagen intimal and medial deposits during the reparatory phases; radiation also has a prothrombotic effect, as an increased deposition or release of von Willebrand factor has been noticed after irradiation of endothelial cells in vitro.[4]

Radiation-induced coronary lesions have several clinical characteristics that differentiate them from classical atherosclerosis; they tend to be localized proximally or at the ostial level, usually with normal distal vessels, with a propensity for the left main coronary artery, left anterior descending artery ostium and right coronary artery ostium. This is due to the inclusion of these parts in the radiation field[4,11-13] during radiotherapy for mediastinal lymphoma or breast cancer (Figure 4).

In the reported case, the patient had a history of mantle field thoracic irradiation, nowadays an outdated treatment technique because of the long-term increased risk of cardiovascular involvement.[12,14] The isolated os-

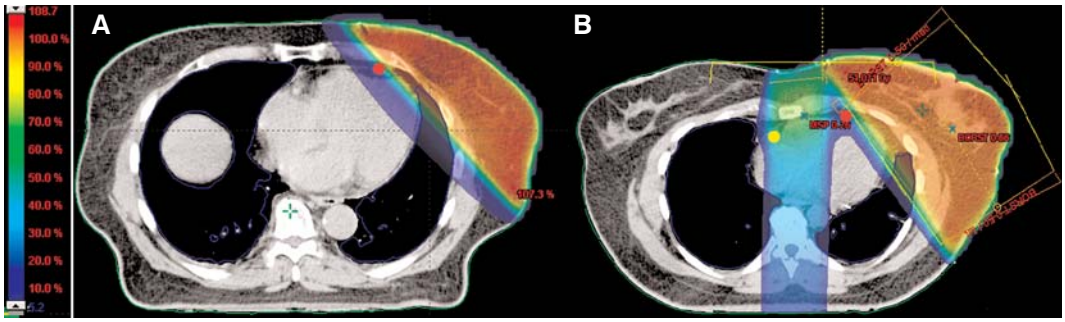

Figure 4. Treatment planning CT for left side breast cancer without (A) and with (B) involvement of the internal mammary and medial supraclavicular lymph nodes, with superimposed radiation field (color-coded for irradiation dose, Gy). Colored dots for coronary arteries included in the irradiation field: red dot – left anterior descending; yellow dot – right coronary artery.

tial involvement of the left main coronary artery ten years after radiotherapy in a patient with no cardiac risk factors suggests a process of accelerated atherosclerosis as a side effect of thoracic irradiation.[15]

Given the young age of the patient at revascularization, as well as the high risks of unprotected left main coronary artery angioplasty, the decision was made to perform coronary artery bypass grafting and full arterial revascularization was chosen. However, the arterial graft patency at 4 years was in our case inferior to that reported in the literature.[16,17] The explanation might be the poor quality of the IMA in a patient with a history of thoracic radiotherapy. The optimal form of myocardial revascularization for radiation-induced coronary artery disease has not been yet established. In view of the proximal lesions, with normal distal vessels, bypass surgery is a frequent choice. In this situation two difficulties can arise: the more difficult surgical approach because of post-irradiation mediastinal fibrosis, as well as the choice of graft type.[11,18] The thoracic radiotherapy field frequently includes the IMA, which can thus be affected by accelerated atherosclerosis. Iqbal reports finding an internal mammary artery reduced to a fibrotic thread. Therefore, most groups have reported using saphenous venous grafts,[11,18,19] but the available data come from small series or case reports. Moreover, these patients are usually young, so that long-term graft patency is a particularly important issue. Nasso et al[20] published a study of 98 patients, half with radiotherapy history (but with a radiotherapy to cardiac surgery time of 395 ± 84 days) and half without radiotherapy, who underwent coronary revascularization using at least one IMA. The short- and medium-term (18 months' follow up) results showed no difference between the two groups. However, there still are no data regarding long-term graft patency.

In our case, the ischemic symptomatology reappeared as unstable angina 4 years after the surgical revascularization, with evidence of more severe native coronary atherosclerosis as well as dysfunction of the arterial grafts. A percutaneous revascularization approach was preferred over the surgical option because of the risks associated with redo surgery, especially after mediastinal irradiation, and the limited options with regard to available conduits (an episode of right calf vein thrombosis in the past history, other arterial conduits with known lower long-term patency versus IMA). Coronary angioplasty is a viable alternative in these patients[13] and was successfully performed in our patient.

Another less frequently documented deleterious cardiac effect of radiotherapy is the development of conduction abnormalities (e.g. permanent or transient bundle branch block or various degrees of atrioventricular block), with some patients requiring a permanent pacemaker. The mean interval between treatment and the appearance of heart block is 12 years (limits 10-15 years).[9,21]

In the present case, several radiotherapy complications occurred in the same patient more than 10 years after oncological remission: accelerated coronary atherosclerosis, vascular involvement of IMA, and conduction tissue involvement with complete heart block.

Oncological disorders associated with long-term survival after remission sometimes present particular problems, as even the most modern oncological therapies can lead to a secondary serious illness, such as a second neoplasm or cardiovascular disorder, a situation placing both patient and physician "between Scylla and Charybdis". This case study highlights the importance of cardiovascular follow up in patients with a history of thoracic radiotherapy, especially when old techniques were used, as well as the difficulties in the choice of the

coronary revascularization method in such a patient. Several groups now advocate the active long-term cardiovascular screening of patients after radiotherapy, using rest and stress electrocardiography and echocardiography.[22-24]

References

1. Heidenreich PA, Kapoor JR. Radiation induced heart disease: systemic disorders in heart disease. Heart. 2009; 95: 252-258.
2. Schultz-Hector S, Trott KR. Radiation-induced cardiovascular diseases: is the epidemiologic evidence compatible with the radiobiological data? Int J Radiat Oncol Biol Phys. 2007; 67: 10-18.
3. Basavaraju SR, Easterly CE. Pathophysiological effects of radiation on atherosclerosis development and progression, and the incidence of cardiovascular complications. Med Phys. 2002; 29: 2391-2403.
4. Sebag-Montefiore D, Hope-Stone H. Radiation induced coronary heart disease. Br Heart J. 1993; 69: 481-482.
5. Clarke M, Collins R, Darby S, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005; 366: 2087-2106.
6. Mauch P, Kalish LA, Marcus KC, et al. Long-term survival in Hodgkin's disease: relative impact of mortality, second tumors, infection and cardiovascular disease. Cancer J Sci Am. 1995; 1: 33-42.
7. King V, Constine LS, Clark D et al. Symptomatic coronary artery disease after mantle irradiation for Hodgkin's disease Int J Radiat Oncol Biol Phys. 1996; 36: 881-889.
8. Hancock SL, Donaldson SS, Hoppe RT. Cardiac disease following treatment of Hodgkin's disease in children and adolescents. J Clin Oncol. 1993; 11: 1208-1215.
9. Adams MJ, Lipshultz SE, Schwartz C, Fajardo LF, Coen V, Constine LS. Radiation-associated cardiovascular disease: manifestations and management. Semin Radiat Oncol. 2003; 13: 346-356.
10. Adams MJ, Hardenbergh PH, Constine LS, Lipshultz SE. Radiation-associated cardiovascular disease. Crit Rev Oncol Hematol. 2003; 45: 55-75.
11. Vondermark D, Seufert I, Schwab F, et al. 3-D reconstruction of anterior mantle-filed techniques in Hodgkin's diasease survivors: doses to cardiac structures. Radiation Oncology. 2006; 1: 10.
12. Rakhit DJ, Becher H, Monaghan M, Nihoyannopoulos P, Senior R. The clinical applications of myocardial contrast echocardiography. Eur J Echocardiogr. 2007; 8: S24-29.
13. Orzan F, Brusca A, Conte MR, Presbitero P, Figliomeni MC. Severe coronary artery disease after radiation therapy of the chest and mediastinum: clinical presentation and treatment. Br Heart J. 1993; 69: 496-500.
14. Gyenes G. Radiation-induced ischemic heart disease in breast cancer—a review. Acta Oncologica. 1998; 37: 241-246.
15. El-Menyar AA, Al Suwaidi J, Holmes DR. Left main coronary artery stenosis: state-of-the-art. Curr Probl Cardiol. 2007; 32: 103-193.
16. Chikwe J, Beddow E, Glenville B. Cardiovascular surgery. Oxford University Press 2006; pp 292-324.
17. Eagle KA, Guyton RA, Davidoff R et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). Circulation. 2004; 110: 1168-1176.
18. McEniery PT, Dorosti K, Schiavone WA, Pedrick TJ, Sheldon WC. Clinical and angiographic features of coronary artery disease after chest irradiation. Am J Cardiol. 1987; 60: 1020-1024.
19. Iqbal SM, Hanson EL, Gensini GG. Bypass graft for coronary arterial stenosis following radiation therapy. Chest. 1977; 71: 664-666.
20. Nasso G, Canosa C, De Filippo CM, et al. Thoracic radiation therapy and suitability of internal thoracic arteries for myocardial revascularization. Chest. 2005; 128: 1587-1592.
21. Knight CJ, Sutton GC. Complete heart block and severe tricuspid regurgitation after radiotherapy. Case report and review of the literature. Chest. 1995; 108: 1748-1751.
22. Heidenreich PA, Hancock SL, Lee BK, Mariscal CS, Schnittger I. Asymptomatic cardiac disease following mediastinal irradiation. J Am Coll Cardiol. 2003; 42: 743-749.
23. Heidenreich PA, Schnittger I, Strauss HW, et al. Screening for coronary artery disease after mediastinal irradiation for Hodgkin's disease. J Clin Oncol. 2007; 25: 43-49.
24. Jurcut R, Wildiers H, Ganame J, D'hooge J, Paridaens R, Voigt J-U. Detection and monitoring of cardiotoxicity-what does modern cardiology offer? Support Care Cancer. 2008; 16: 437-445.