Cardiologia Hungarica 2008; 38 : 336–343

Myocardial lesions in long-term survivers of Hodgkin disease; an echocardiographic and dual isotope F-18 FDG/Tc-99m MIBI SPECT study

Zsófia Simon, Ildikó Garai[1], Judit Végh, Zsófia Miltényi, József Varga[1], Lajos Szabados[1], László Galuska[1], Árpád Illés

DEOEC, Institute of Internal Medicine, 3rd Department of Internal Medicine,
[1]Department of Nuclear Medicine, Debrecen
[2]PET-CT Medical and Diagnostic Ltd.

Address for correspondence:
Simon Zsófia
H-4032 Debrecen, Móricz Zs. krt. 22.
Tel/Fax: (+36-52) 414-969
E-mail: zsocogo@gmail.com

Keywords:
DISA, Hodgkin lymphoma, late cardiac complications, quality of life, survival

Introduction: *By using modern treatment modalities, the survival of Hodgkin lymphoma patients is getting better; they are cured and that is why late complications have come to the focus. Among them, cardiovascular complications have the highest risk besides second malignancies.*
Aims: *To survey the incidence and seriousness of myocardial damage of our Hodgkin lymphoma patients.*
Patients and methods: *Data of 76 Hodgkin lymphoma patients, who had been in complete remission for at least five years and may or may not experienced chest pain, were analyzed. We assessed their conventional cardiovascular risk factors and the applied anticancer treatment; we also performed resting and stress ECG, echocardiography, and F-18 FDG/Tc-99m MIBI DISA SPECT tests.*
Results: *Based on the results of the DISA test, the patients were divided into two groups: 42 patients had perfusion and/or metabolic myocardial lesions, among them there were more males, but as for the age, risk factors, and the applied treatment, they did not differ significantly from those whose DISA test was negative. Positive DISA tests showed significant correlation with chest pain. Mostly the anterior and inferior segments were affected. The type of the lesion did not correlate with the treatment modality.*
Conclusions: *Both perfusion and metabolic derangement of the myocardium can cause chest pain and affect the quality of life. DISA test is a sensitive method used in detecting myocardial dysfunction. It can help us with the differentiation of metabolic disorders and small or large vessel diseases causing chest pain, the latter of which may need intervention.*

The treatment for Hodgkin lymphoma showed a significant change in the past few decades. The previously lethal illness became curable in most cases. Long-term survival data are more favorable: according to international and our own data, the ten-year prognosticatory survival of the disease is more than 80% (1, 2). For this reason, the late complications of the disease and/or its treatment got highlighted in the past few decades, including second malignancies and cardiovascular complications that have the highest, life threatening risk (3). Their frequency increases in the post-treatment period and statistics show that about 15 years later the main cause of death is not the underlying disease itself but its complications (4).
Hodgkin lymphoma patients may develop various cardiac complications part of which may be detected acutely during or shortly after the treatment (pericarditis, pancarditis), others are manifested only some years or decades later (valvulopathy, ischaemic/toxic cardiomyopathy, myocardial infarction, conduction disorders). The main causes of these complications are mostly chest irradiation and anthracyclin-based chemotherapy. Although the prevalence of heart diseases developing due to mediastinal irradiation is unknown, international literature calculates with a rate of 6-30%, while the occurrence of coronary artery disease (CAD) is 5.5-12% (5, 6).
As cardiac and vascular diseases – especially myocardial infarction – influence the life expectancy and quality of life, great emphasis is placed on prevention as well as early diagnosis which may be the key to adequate therapy. Besides traditional cardiac screening, various isotope diagnostic methods also play an important part in this. The sensitivity of Tl-201 and Tc-99m MIBI

scintigraphy is excellent in the detection of CAD–more than 90% (7). Myocardial viability is more frequently assessed by F-18 fluorodeoxyglucose (FDG) positron emission tomography or alternatively by single photon emission tomography (SPECT) (8, 9). Our objective was to assess the perfusion and metabolic lesions of the myocardium among Hodgkin lymphoma patients who survived for long or recovered from the disease.

Patients and methods

Seventy-six Hodgkin lymphoma patients were included in the study, who were treated and followed up at the 3rd Department of Internal Medicine of DEOEC between 1970–2000 or later. The study was conducted in 2006 at our clinic and the Department of Nuclear Medicine. The patients included were in complete remission for at least five years and did or did not have chest pain. However, body mass index (BMI) greater than 30 and unstable diabetes were set as exclusion criteria. The treatment consisted of radiation therapy, chemotherapy, or the planned combination of both (CMT) according to the current national and international guidelines. In accordance with the Hungarian recommendations, extended field radiation therapy (EFRT; total nodal, mantle field, inverted Y) was applied until the second half of the 1990s with the Hungarian-made Gravicert telecobalt device as the source of radiation. This method was not suitable for covering large fields; therefore an additive technique described by Stricstrock and Musshoff was used for simultaneous treatment of the lymphatic regions below and above the diaphragm with a cumulative dose of 40-44 Gys. The mantle and inverted Y fields consisted of multiple parts *(Figures 1 and 2).* The focal dose was calculated at the center of the body. Due to the length of the treatment and the lack of capacity, daily radiation was delivered only from a single direction. At the beginning, field matching was carried out manually, later it was computer-driven, based on the isodose distribution measurements. From 2000, patients are treated with involved field radiation therapy (IFRT) using an SL18 multileaf collimator on a linear accelerator. Based on the national and international recommendations, the initial average cumulative dose of 40–44 Gys was reduced to a total of 30-36 Gys in the last decade. Until 1990, mainly the CV(O)PP (cyclophosphamide, vinblastine (vincristine), procarbazine, prednisolone) chemotherapy protocol was used. It was replaced with COPP/ABV (cyclophosphamide, vinblastine, procarbazine, prednisolone/adriamycin, bleomycin, vinblastine), while since 1997, the ABVD (adriamycin, bleomycin, vinblastine, dacarbazin) regime has been applied. In the patients' medical history, we recorded data concerning smoking habits and concomitant diseases, paying special attention to hypertension and diabetes mellitus as cardiovascular risk factors, as well as premature menopause in the case of women. The anamnestic and treatment data were processed using the MedSolution medical informational database and the patients' records. Blood chemistry tests were used to assess the patients' thyroid function and their glucose, blood lipid, and uric acid level. Cardiac tests included a 12-lead rest ECG and a Bruce protocol stress ECG (cycle ergometry) as well as echocardiography performed with a Hewlett Packard, Sonos 5500 cardiac ultrasound system and an S4 transducer. The internationally accepted parasternal long- and short-axis views and the apical four-chamber views were used with the patients in the standard left lateral decubitus position. Besides measuring the size of the heart chambers, we assessed the segmental wall motion abnormalities (concerning 16 segments), determined the left ventricular ejection fraction and

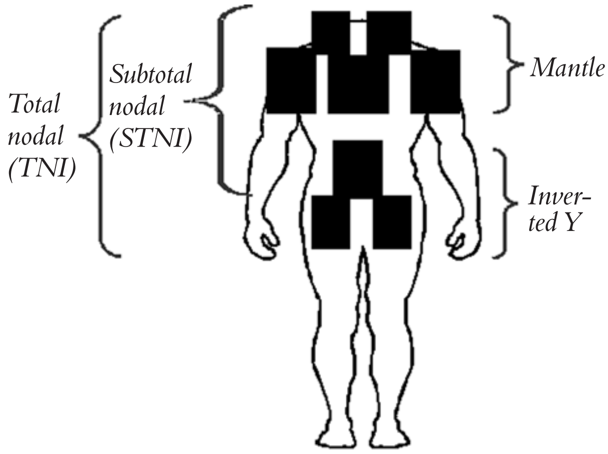


Figure 1. The lymphatic regions of Hodgkin lymphoma patients affected by extended field radiation therapy

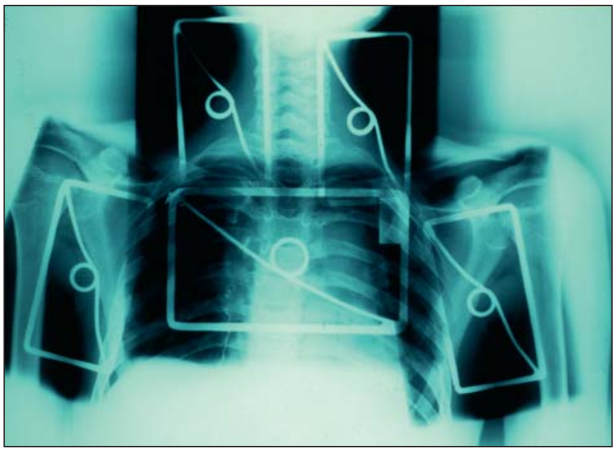


Figure 2. The additive technique used during mantle field irradiation

examined the left ventricular diastolic function with pulsatile Doppler technique. Invasive tests (coronary angiography) were performed at the discretion of the treating cardiologis.

Patient preparation

Patients were asked to refrain from taking rich food the day before the examination, while on the day of the test, they were allowed to have a light breakfast. Each patient received 80 mg glucose and 250 mg acipimox (Olbetam, Pharmacia, Hungary) per os 1.5-2 hours before administering IV F-18 fluorodeoxyglucose (FDG) to raise the blood glucose level and decrease the free blood lipid level for the optimal FDG recording of the myocardium. Ten minutes after the IV injection of 370 MBq F-18 FDG, 850-900 MBq Tc-99m MIBI was injected. Scanning started 60 minutes later.

Acquisition

Acquisition was performed in single-head mode with an APEX HELIX dual-head gamma camera (Elscint) fitted with an ultra-high energy (511 keV) collimator simultaneously on two energy channels (Tc-99m: 140 keV±10%, F-18: 511 keV±10%) in a 64×64 matrix (pixel size: 6.925 mm) at 180° from 45° RAO to 45° LPO (at every 3°). Scanning time was 30 sec per view.

Image processing

The results were processed with a dedicated 511 keV software package (Elscint). Metz filtering and filtered back projection were applied during reconstruction. Based on the Tc-99m MIBI images, three raws of slices were taken (parallel to the left ventricular short axis, horizontal long axis, and vertical long axis) identically to the FDG images as well. The polar map was constructed from the short-axis slices based on both radiopharmacon distributions. The polar map shows the average activity (%) of 16 regions relative to the highest activity segment *(Figure 3)*. From among scintigraphic parameters, we assessed the relative radiopharmacon recordings (MIBI and FDG) per segments, the lowest perfusion and metabolic percentage value between segments, and the maximum deviation between relative metabolism and relative perfusion.

Statistical analysis

The aim of our analysis was to reveal whether myocardial perfusion and metabolic changes show any correlation with the patients' symptoms or the abnormalities found using simple non-invasive cardiac tests (chest pain, stress ECG, echocardiography), the type of the therapy (chemotherapy – paying special attention to anthracyclin-based chemotherapy –, radio-

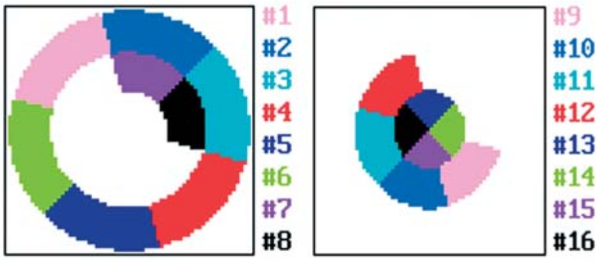


Figure 3. The polar map can demonstrate the average activity of 16 regions

therapy, and CMT), as well as diabetes mellitus as a cardiovascular risk.
Statistical calculations were made using the SPSS program suite. The normality of the data groups was checked with the Kolmogorov-Smirnov test, while Levene's test was used to assess the equality of variance. The average values of two age groups were usually compared with t-test; in case of unequal variances, d-test was used. For multiple comparisons, the Bonferroni correction was used for per-segment analysis. The differences were considered significant below the probability level of 0.0032. Variance analysis was used to compare the three treatment groups.

Results

The mean age of the 76 Hodgkin lymphoma patients (33 females, 43 males) was 29.9 (9–63) at the detection of the disease and the beginning of the treatment. For the total duration of the study period, the mean age was 45.8 (25–74). The time elapsed between the treatment and the DISA test was 16.1 (5–33) years on the average. The patients were divided into two groups based on the DISA results. Myocardial perfusion and/or metabolic disorders were observed in 42 patients, they were classified as DISA positive. The 34 patients not exhibiting abnormalities composed the DISA negative group. For details about the patients' demographic characteristics, treatment data, and the prevalence of the traditional cardiovascular risk factors, see *Figure 1.* The number of males was higher in the DISA positive group, but the difference was not significant. In most cases, perfusion and metabolic disorders occurred simultaneously, though only perfusion damage was seen in 12 patients and only metabolic damage was observed in 6 patients.

Correlation between the results of the non-radioisotopic examinations and the method of treatment

The results of the cardiac tests are shown in *Table 3.* Although more than half of the patients complained of chest pain, significant ischaemic changes were revealed

Table 1. General characteristics, therapy used during treatment, and the incidence of traditional atherogenic risk factors depending on the results of the DISA examination in 76 Hodgkin lymphoma patients (RT: radiotherapy, CT: chemotherapy, DISA: dual-isotope simultaneous acquisition SPECT) The assessed parameters showed no significant difference in the two groups

Characteristics	DISA positive	DISA negative	Total number of patients
Number of patients (males/females)	42.0 (11/31)	34.0 (22/12)	76.0 (33/43)
Mean age at the diagnosis (years)	29.6 (9–57)	30.3 (14–63)	29.9 (9–63)
Mean age at the time of DISA (years)	46.4 (30–73)	45.2 (25–74)	45.8 (25–74)
Time between the diagnosis and DISA (years)	16.6 (6–33)	15.5 (5–33)	16.1 (5–33)
Treatment			
Medastinal RT	7	2	9
Mediastinal RT+CT/anthracyclin	26/11	18/10	44/21
CT/anthracyclin±non-mediastinal	9/5	14/8	23/13
Risk factors (abnormal values in % of patients)			
Hypertension	46.7	36	42.9
Diabetes mellitus	9.1	17.4	11.9
Hypercholesterinaemia	57.5	62.5	58.9
Hyperuricaemia	35.7	25	33.3
Hypothyreosis	33.3	40.6	36.4
Smoking	47.8	40	46.4
In females: premature menopause	18 (2/11)	9 (2/22)	12 (4/33)

Table 2. The incidence of perfusion and/or metabolic damages during the DISA examination in the various treatment groups (RT: radiotherapy, CT: chemotherapy)

Damage	Perfusion	Metabolic	Both
Medastinal RT	4	–	3
Medastinal RT+CT	7	3	16
CT±non-mediastinal RT	1	3	5
Total	12	6	24

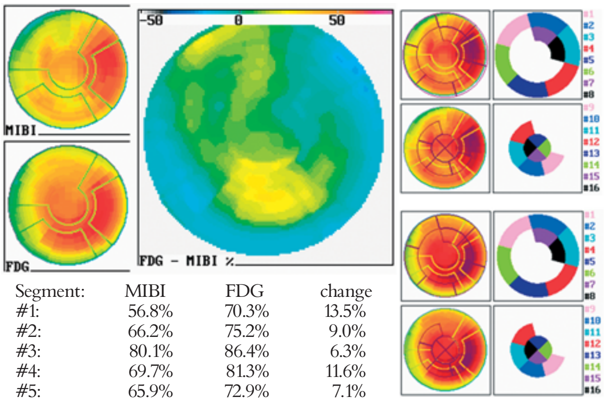
only in a few cases during the non-invasive examination. However, diastolic dysfunction was detected with echocardiography in almost 40% of the cases and its development showed correlation with the method of treatment: it occurred in 44% of patients under irradiation, in 43% of patients under thoracic irradiation as well as chemotherapy, and only in 26% of patients not receiving thoracic irradiation. The difference was considerable but not significant (p=0.349).

Correlation between the results of the non-radioisotopic tests and the symptoms

In patients exhibiting chest pain, myocardial perfusion was significantly lower in the inferoapical and anteroseptal regions (in segments 10, 14, 15, and 16, p values were 0.0002, 0.0015, <0.0001, and 0.0029, respectively) (Figures 4 and 5). Glucose metabolism was impaired in segments 9 and 10 (p values: 0.0007, 0.0001). The difference in the relative values of perfusion and metabolism was not significant anywhere. The alterations during the stress test and the echocardiographic examinations did not go together with significant

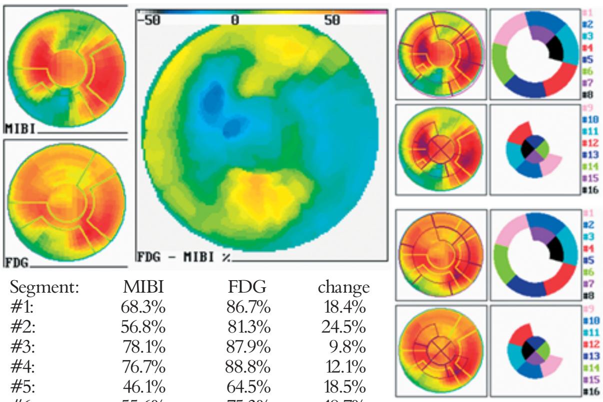
Table 3. Abnormalities revealed by cardiac tests in the light of the DISA test (ECG: electrocardiogram, PTA: percutaneous transluminal coronary angiography, PTCA: percutaneous transluminal coronary angioplastica, DISA: dual-isotope simultaneous acquisition SPECT)

Clinical findings	DISA positive	DISA negative	Total number of patients
Chest pain	39	4	43
ECG changes at rest	10	1	11
Ischaemic change during cycle ergometry	9	2	11
Wall motion disorder during echocardiography	10	2	12
PTA/PTCA	5	1/negative	5+1



Segment:	MIBI	FDG	change
#1:	56.8%	70.3%	13.5%
#2:	66.2%	75.2%	9.0%
#3:	80.1%	86.4%	6.3%
#4:	69.7%	81.3%	11.6%
#5:	65.9%	72.9%	7.1%
#6:	62.4%	62.1%	–0.3%
#7:	81.4%	85.9%	4.5%
#8:	100.0%	100.0%	–0.0%
#9:	87.0%	99.8%	12.8%
#10:	77.6%	96.6%	19.0%
#11:	76.9%	82.8%	5.9%
#12:	79.6%	86.8%	7.2%
#13:	86.9%	91.5%	4.5%
#14:	88.2%	92.7%	4.5%
#15:	78.8%	94.5%	15.7%
#16:	84.6%	93.8%	9.3%

Figure 4. A maintained myocardial perfusion and FDG recording of a 54-year-old woman who received combined chemo- and radiotherapy (mantle field irradiation) 14 years ago



Segment:	MIBI	FDG	change
#1:	68.3%	86.7%	18.4%
#2:	56.8%	81.3%	24.5%
#3:	78.1%	87.9%	9.8%
#4:	76.7%	88.8%	12.1%
#5:	46.1%	64.5%	18.5%
#6:	55.6%	75.3%	19.7%
#7:	67.1%	76.3%	9.2%
#8:	97.6%	88.6%	–9.0%
#9:	93.6%	100.0%	6.4%
#10:	55.5%	79.3%	23.8%
#11:	98.6%	94.1%	–4.4%
#12:	94.8%	85.1%	–9.7%
#13:	87.7%	79.8%	–7.9%
#14:	87.0%	87.1%	0.1%
#15:	85.5%	86.5%	1.0%
#16:	100.0%	84.3%	–15.7%

Figure 5. Reduced activity on the inferior wall of the left ventricle in a 50-year-old woman who received chemotherapy and mantle field irradiation 27 years ago

myocardial perfusion and metabolic changes in any regions. Only the maximum difference between relative perfusion and metabolism reached the significance limit (p=0.049) with the abnormal echocardiography records.

Correlation between the results of the radioisotopic tests and the method of treatment

Relative segmental perfusion, metabolic rates, and the difference of these two showed no significant variation in any segments. However, the minimal value of perfusion was significantly lower (p=0.0314) in the group receiving radiotherapy.

The positivity of the DISA test showed unambiguous and significant correlation with the prevalence of chest pain. Based on the results, the cardiologist indicated coronarography for 6 patients; one of them had no significant coronary stenoses, one had triple-vessel disease, so a CABG procedure was performed, and 4 patients had stent implantation, RCA was stented in 2, Cx in 1, and LAD also in 1 case. One patient presumably developed in-stent restenosis at the region of the RCA, which caused acute myocardial necrosis in inferior localization.

The test results of the 76 patients were analyzed from a different point of view as well: if echocardiography or the isotope technique revealed some myocardial damage (44 cases), the patient belonged to group 1, while the patients with negative results (32 cases) were classified as members of group 2. We examined whether the frequency of the confirmed myocardial damage is dependent of the method of treatment (mediastinal irradiation±chemotherapy, chemotherapy±non-mediastinal irradiation) but no significant correlation was found in this respect.

Discussion

The widespread use of high-dose radiotherapy in the 1950s and polychemotherapy in the 1970s meant great success in the treatment of Hodgkin lymphoma patients. The so-far lethal disease became potentionally curable and today the total 10-year predictable survival is more than 80% (1, 2). At the same time, there was a change in approach – the initial illness- and treatment-oriented approach was replaced with a patient-oriented (risk adapted) therapeutic aspect. One of the main causes of this change was that late complications arising from the illness itself and/or from its treatment came to the foreground with the improvement of the long-term survival rate including second malignancies and cardiovascular complications that are the most frequent and severe ones influencing life expectancy and the quality of life to a great extent (3–5). Aleman et al. examined a great number of Hodgkin lymphoma patients who had been treated before the age of 41 and had been in complete remission for at least five years. The results revealed that the incidence of cardio-vascular (CV) diseases was 3-5 times higher than that of the average population, that is, 66-80% of the CV diseases in this group were caused by the lymphoma treatment. It was emphasized that morbidity resulting from CV diseases was much more significant than mortality (10). Our own study also revealed that although cardiac damages of some extent were detected in more than half of our patients (without assessing valvulopathies and right ventricular abnormalities in this study as these were presented in our former publications) these changes were significant only in few of the cases.

The cardiac damages of Hodgkin lymphoma patients are of various types – irradiation and chemotherapy playing a decisive role in this. It is well known from the cases of mammary carcinoma and Hodgkin lymphoma patients that irradiation does cause myocardial impairment. The estimated rate of the incidence of cardiac damages caused by irradiation is 6-30%, while the prevalence of the coronary disease is 5.5-12% among the Hodgkin lymphoma patients in various studies (5). Myocardium as a tissue of slow cell division was considered resistant to irradiation for a long time; later it was proved to be severely damageable by the extended effects of irradiation. Several mechanisms can lead to increased atherosclerosis; it is presumed that intima injury and consequential lipid accumulation cause fibrotic hyperplasia (11). Other studies point out that irradiation induces endothelial dysfunction (12), fibrosis-inducing cytokine evolution (TNF, IL-1, IL-6, IL-8, PDGF, TGF-alpha) (13, 14), disorders in the synthesis and evolution of nitrogen oxide (15), and upregulation of the endothelial adhesion molecules (16). These factors together with the inflammatory response to radiation play a part in the initiation and progression of atherosclerosis, vascular fibrosis, and hyperplasia that may finally lead to a thrombotic event (16). The factors responsible for the formation of cardiac radiation damage include cumulative radiation dose, single radiation load delivered, radiated heart volume, and the distance of the heart from the thoracic wall (5, 17). The atherogenic effect of radiotherapy is supported by the fact that the value of minimal perfusion was significantly lower in the group of radiated patients than in the ones not receiving radiotherapy. The incidence and the severity of coronary diseases are further increased by the traditional CV risk factors including hypertension, diabetes mellitus, smoking, and hypercholesterinaemia, the last being adversely affected by hypothyreosis frequently occurring in Hodgkin lymphoma patients (the thyroid region is within the mantle field, so it is damaged by irradiation which leads to reduced functioning) (18). Among our patients, perfusion disorder at rest occurred mainly on the inferior wall and in the basal segments that could be affected both in the mantle and the inverted Y fields; the location of the perfusion disorder is similar to the one experienced by *Gyenes et al.* after the radiotherapy of mammary carcinoma patients. The studied cases did not reveal any correlation between the above-mentioned risk factors and DISA positivity. It may be explained by the fact that even the smallest abnormalities in the lab test results were considered positive, no differentiation was made between small degree and severe hypercholesterinaemia, and that blood pressure and blood glucose were closely controlled. The results of Aleman et al. also reinforced that in cases of treated hypertension, irradiation-induced CV risks are not higher compared to the control population (10). *Glanzman et al.* also concluded that if no traditional CV risks (smoking, diabetes mellitus, hypertension, obesity, hypercholesterinaemia) are present, irradiation does not imply increased CV risks (18). All these lead to the conclusion that the efficient treatment of the traditional risk factors must be of key importance in this patient group. The data of long-term follow-up show that increased CV risks can be detected even after 25 years and the risks are higher in patients who were younger than 25 at the time of the treatment (10, 19).

The study of *Schömig et al.* proved that high atherogenic diathesis is long-lasting and difficult to manipulate. The aim of this study was to assess the incidence of in-stent restenosis in a large number of patients having coronary intervention and stent implantation by performing control coronarography 6 months after the intervention. The patients were divided into three groups: lymphoma patients receiving mediastinal irradiation, lymphoma patients not receiving irradiation, and non-lymphoma patients without irradiation. The rate of in-stent restenosis in the mediastinal irradiation group was more than 80%, while it was about 20% in the two other groups. This observation suggests that this high-risk group should be predestined to have drug-eluting stents implanted (16). Coronarography was performed in 76 of our patients and 5 had positive results. Four of them had stent implantation, and in-stent restenosis was presumed in one case without performing recoronarography. This 1 patient received mediastinal radiotherapy as well as anthracyclin based chemotherapy, and he belonged to the high-risk group concerning traditional CV risk factors (hypertension, diabetes mellitus). On the fifth patient, coronary bypass operation was performed. The prior DISA test was positive in all the 5 cases.

Besides traditional risk factors, cardiac damage caused by irradiation may be intensified by anthracyclin-based polychemotherapy as well. The cardiotoxic effect of the anthracyclins (doxorubicin, daunorubicin, epirubicin, etc.) is well known. Observations gained through children's examinations show that the toxic effect correlates with the cumulative dose. In adults, the age of the patients also plays a part. In adult patients, toxic effect is expected above the cumulative dose of 480 mg/m^2, and it certainly occurs above 800 mg/m^2; toxic effect is caused by the direct damage of the myoepithelium (10, 19, 20). Dexrazoxane, the free-radical scavenger, could be used in primary and secondary prevention; though some authors argue that it reduces the efficiency of chemotherapy (10, 20). Regarding our cases, no cardiomyopathy or heart failure deriving definitely from anthracyclin toxicity occurred, which can mainly be explained by the fact that our patients rarely received doxorubicin treatment with a cumulative dose above 400 mg/m^2, and such treatments were applied mainly in the second half of the 1990s (ABVD protocol), so its complications will probably arise later. Drawing a distinction between anthracyclin-based and irradiation-induced myocardial damage is not an easy task. Fibrosis caused by irradiation may lead to cardiomyopathy which can be detected as severe diastolic dysfunction by echocardiography but it is certainly not specific to irradiation damage (21). The incidence of diastolic dysfunction detected by echocardiography was significant more than one third of the patients were affected. At the same time, this abnormality was observed in more than 40% of the patients receiving thoracic irradiation but only in 26% in cases lacking thoracic irradiation. This difference is unequivocally connected to the presence or absence of mediastinal radiotherapy and it is considerable but not significant. Anthracyclin-induced cardiomyopathy is manifested as systolic dysfunction that can be assessed by echocardiography expressed by the value of fractional shortening and its variance (20). As no such data were recorded before treatment, these kinds of measurements were not taken.

Vinca alkaloids may have cardiotoxic effects as well and bleomycin may also cause adverse cardiac events indirectly through the right ventricular pressure increase induced by pulmonary fibrosis (19), but these abnormalities were not examined in the present study.

So it is known that Hodgkin lymphoma treatment may lead to various CV complications. International studies and our own observations both reveal that these complications are of different severity but never to be ignored, as they can progrediate very fast in a short time (10, 16, 19). Present research aims at risk reduction (primary and secondary prevention) as well as developing a diagnostic procedure for screening high-risk patients from this elevated-risk group (10). Although the sensitive methods used in the last few decades like stress echocardiography, radionuclide assessment of left ventricular function, spiral CT scans appropriate for detecting coronary artery calcification, and the combination of these examinations are efficient, none of them had complete success in this application (22–24). DISA test used in this study provided the possibility of distinguishing between chest pains induced by metabolic and perfusion disorders. Though DISA is a suitable method for screening the majority of macroangiopathy patients who can undergo intervention, this kind of sensitivity of the method could be increased by physical/chemical stress.

Conclusions

In summary, we can conclude that risk of CV diseases among cured Hodgkin lymphoma patients is high and influences the quality and expectancy of life so screening, early detection, and effective therapy are of great importance in these cases. The possible solutions for macroangiopathy are coronary intervention and drug-eluting stent implantation, while the treatment for microangiopathy and metabolic disorder includes the improvement of metabolism (diets, lifestyle changes, stabilizing the carbohydrate metabolism and the lipid profile, administering trimetazidine). In recently diagnosed lymphoma patients, risk-adapted treatments should be favored and therapeutic toxicity should be reduced. All these are supported by the interim FDG PET/CT scans as well as echocardiography that may be used before or, if necessary, during treatment mainly in elder patients and advanced cases (6-8 cycles of ABVD expected, significant anthracyclin load). Depending on the results, the less cardiotoxic EBVD (epirubicin) protocol can be applied. In addition, patient education and efficient control of blood pressure, blood glucose, and cholesterol are crucial.

References

1. Diehl V, Mauch P, Connors JM. Hodgkin's lymphoma. Hematology 1999. p. 270–289.
2. Simon Z, Keresztes K, Miltényi Z, et al. Our experiences in treating patients with Hodgkin disease in the last decade Orv Hetil 2007; 148 (15): 675–682.
3. Aleman BMP, van den Belt-Dusebout AW, et al. Long-term cause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol 2003; 21: 3431–3439.
4. Henry-Amar M, Somers R. Survival outcome after Hodgkin's disease: a report from the international data base on Hodgkin's disease. Semin oncol 1990; 17: 178–193.
5. Miltényi Zs, Keresztes K, Garai I, et al. Radiation-induced coronary artery disease in Hodgkin's disease. Cardiovasc Radiat Med 2004; 5: 38–43.
6. 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.
7. Kapur A, Latus KA, Davies G, et al. A comparison of three radionuclide myocardial perfusion tracers in clinical practice: the ROBUST study. Eur J Nucl Med Mol Imaging 2002; 29 (12): 1608–1616.
8. Ghesani M, Depuey EG, Rozanski A. Role of F-18 FDG positron emission tomography (PET) in the assessment of myocardial viability. Echocardiography 2005; 22 (2): 165–177.
9. Matsunari I, Kanayama S, Yoneyama T, et al. Electrocardiographic-gated dual-isotope simultaneous acquisition SPECT using 18F-FDG and 99mTc-sestamibi to assess myocardial viability and function in a single study. Eur J Nucl Med Mol Imaging 2005; 32(2): 195–202.
10. Aleman BMP, van den Belt-Dusebout AW, De Bruin ML, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood 2007; 109 (5): 1878–1886.
11. Gold H. Production of arteriosclerosis in the rat. Effect of x-ray and high-fat diet. Arch Pathol 1961; 71: 268–273.
12. Fajardo LF. The unique physiology of endothelial cells and its implications in radiobiology. Front Radiat Ther Oncol 1989; 23: 96–112.
13. Kruse JJ, Zurcher C, Strootman EG, et al. Structural changes in the auricules of the heart after local ionising irradiation. Radiother Oncol 2001; 58: 303–311.
14. Gyenes G. Radiation induced ischemic heart disease in breast cancer. Acta Oncol 1998; 37: 241–246.
15. Sugihara T, Hattori Y, Yamamoto Y, et al. Preferential impairment of nitric axid-mediated endothelium-dependent relaxation in human cervical arteries after irradiation. Circulation 1999; 10: 635–641.
16. Schömig K, Ndrepepa G, Mehilli J, et al. Thoracic radiotherapy in patients wirh lymphoma and restenosis after coronary stent placement. Catheter Cardiovac Intervent 2007; 70: 359–365.
17. Garling B, Gottiener J, Borer JS. Cardiovascular complications of the treatment of Hodgkin's disease. In: Lacher JS, Redman JS, editors. Hodgkin's disease: the consequences of survival. Philadelphia: Lea & Febiger; 1990. p. 267–95.
18. Glanzmann C, Kaufmann P, Jenni R, et al. Cardiac risk after mediastinal irradiation for Hodgkin's disease. Radither Oncol 1998; 46: 51–62.
19. Swerdlow AJ, Higgins CD, Smith P, et al. Myocardial infarction mortality risk after treatment for Hodgkin disease: A collaborative British Cohort Study. J Nat Cancer Inst 2007; 99: 206–214.
20. Hequet O, Le QH, Moullet I, et al. Subclinical late cardiomyopathy after doxorubicin therapy for lymphoma in adults. J Clin Oncol 2004; 22: 1864–1871.
21. Adams MJ, Lipsitz SR, Colan SD, et al. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy J Clin Oncol 2005; 23(15): 3634–3636.
22. Suzuki j, Yanagisawa A, Shigeyama T, et al. Early detection of anthracyclin-induced cardiotoxicity by radionuclide angiocardiography. Angiology 1999; 50 (1): 37–45.
23. Heindenreich PA, Schnittger I, Strauss HW, et al. Screening for coronary artery disease after mediastinal irradiation for Hodgkin's disease. J Clin Oncol 2007; 25 (1): 43–49.
24. Apter S, Shemesh J, Raanini P, et al. Cardiovascular calcifications after radiation therapy for Hodgkin lymphoma: computed tomography detection and clinical correlation. Coron Artery Dis 2006; 17 (2): 145–151.