

CARDIAC INJURY AS LATE TOXICITY OF MEDIASTINAL RADIATION THERAPY FOR HODGKIN'S DISEASE PATIENTS

Pier Luigi Zinzani, Filippo Gherlinzoni, Giancarlo Piovaccari^o, Giovanni Frezza*, Maurizio Bendandi, Rossella M. Ferretti^o, Enza Barbieri*, Mauro Fiacchini, Lucio Babini*, Bruno Magnani^o, Sante Tura

Institute of Hematology "Seràgnoli", *Institute of Radiotherapy "L. Galvani", and ^oInstitute of Cardiology, University of Bologna, Italy

ABSTRACT

Background. During the last 20 years Hodgkin's disease (HD) has become one of the most curable neoplasms; in fact, more than 75-80% of patients are expected to achieve long-term relapse-free survival with appropriate therapy. However, overall survival has been affected by intercurrent or treatment-induced diseases such as the increased risk of cardiac toxicity in patients who received mediastinal irradiation.

Methods. The incidence of cardiac abnormalities after mediastinal radiotherapy was assessed in 102 consecutive HD patients who underwent this treatment from January 1970 to December 1980. Basal investigation procedures included electrocardiogram and echocardiography; myocardial perfusion scintigraphy with 201-thallium and coronary arteriography were performed in selected patients.

Results. Eleven patients (10.8%) presented cardiac abnormalities, which were asymptomatic in three cases. Eight cases of myocardial ischemia and 3 of constrictive pericarditis were observed. The incidence of late cardiotoxic effects was related to total mediastinal dose and to the irradiation technique.

Conclusions. The increasing duration of follow-up shows that as mediastinal irradiation increases so does the risk of late cardiotoxic side effects. For this reason, a proper treatment strategy should reduce these risk factors through new combined modality protocols and routine evaluation of cardiologic follow-up.

Key words: Hodgkin's disease, mediastinal irradiation, late cardiac toxicity

First radiation therapy and subsequently successful chemotherapy regimens have permitted physicians to think not merely in terms of 5-10 year survival, but to look forward to complete resolution of Hodgkin's disease (HD) in a high percentage of patients.¹⁻⁴

Owing to the improved efficacy of therapy, the late complications related to curative treatment in long-term survivors are now well recognized. Cardiotoxicity as a late side effect of mediastinal radiotherapy is an important complication of HD treatment. These late effects are a function of the total dose administered to the

cardiovascular system and may occur months to years after radiation. These late sequelae are manifested as tissue fibrosis and necrosis.

Prior studies indicated that mediastinal irradiation causes a wide range of late sequelae, such as different forms of pericarditis, valvular and conduction defects, and coronary artery diseases.⁵⁻²¹ Concerning the risk of myocardial infarction, the literature data are discordant; in fact, some studies have reported a significant risk increase after mediastinal radiotherapy whereas other authors have shown a myocardial infarction rate comparable to that expected in

Correspondence: Pier Luigi Zinzani, M.D., Istituto di Ematologia "L. e A. Seràgnoli", Policlinico S. Orsola, via Massarenti 9, 40138 Bologna, Italy. Tel. international +39.51.390413. Fax. international +39.51.398973.

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the general population. Recently, some studies have offered convincing evidence for an increased risk of coronary artery disease.¹³⁻¹⁵

The aim of this study was to assess the risk of coronary abnormalities after mediastinal irradiation in a subset of 102 HD patients who had received mantle radiotherapy 14 or more years earlier.

Patients and Methods

The individual records of the 102 consecutive patients treated for HD who received mediastinal radiotherapy between January 1970 and December 1980 were reviewed through a cardiological investigation to verify and assess existing data regarding late cardiac toxicity related to curative treatment. These patients comprised 27.5% of the whole series, which consisted of 372 cases.

Staging procedures at diagnosis, including bone marrow biopsy, chest radiography, and evaluation of the abdomen with bipedal lymphangiography and/or abdominal computed tomography scan, were performed according to the Ann Arbor staging system.²²

Patients were considered eligible for the study if the following criteria were met: radiotherapy delivered to the mediastinum; an interval of at least 14 years between the completion of radiation therapy and cardiac evaluation; no history of hypertension, angina pectoris or congestive heart failure prior to the diagnosis of HD; age less than 60 years at diagnosis; informed consent given to take part in the study.

Patient characteristics (Table 1)

At the diagnosis, the median age was 30 years (range 15 to 42); 51 patients were males and 51 females. Nineteen patients presented stage I, 48 stage II, and 35 stage III disease. Eighty-seven had the nodular sclerosis and 15 the mixed cellularity subtype. Concerning the treatment, 16 patients received total nodal irradiation and 86 were administered combined modality treatment consisting of total nodal irradiation or subtotal nodal irradiation or involved field radiotherapy, followed by 3 to 6 courses of the MOPP²³ chemotherapy regimen.

Table 1. Patient characteristics.

Total patients	102
Sex M/F	51/51
Age (years) (at diagnosis):	
• median	30
• range	15-42
Histology:	
• nodular sclerosis	87/102
• mixed cellularity	15/102
Stage:	
• I	19/102
• II	48/102
• III	35/102
Treatment:	
• radiotherapy alone	16/102
• radiotherapy plus chemotherapy	86/102

Table 2. Treatment characteristics of the 102 patients.

Dose:	
• < 45 Gy	21/102
• 45 Gy	78/102
• > 45 Gy	3/102
Technique of irradiation:	
• one field per day	48/102
• both opposing fields per day	54/102

Treatment characteristics (Table 2)

All patients underwent at least full mantle irradiation performed with a ⁶⁰Co unit; the mediastinum was treated with separate AP-PA adjoining fields. Prescribed mediastinal dose, calculated at the midline of the mediastinum along the central axis, was 45 Gy in 78 patients, 36-44 Gy in 21 patients and 46-50 Gy in 3 patients. Daily fractions of 1.2-1.5 Gy were employed; only 2 patients received a daily dose of 2 Gy. Forty-eight patients were treated alternately, i.e. with anterior fields being treated on day one and posterior fields on day two; in 54 patients each field was treated daily.

Cardiologic evaluation

The mean follow-up from completion of

treatment until the time of the study was 210 months (range 160-307). During this period the patients were examined every 3 months during the first year after treatment and every 6 to 12 months thereafter as part of the clinical follow-up of HD. The status of the disease was as follows: 90 patients were in first complete remission, 11 patients in second complete response, and 1 in third complete remission.

Cardiologic evaluation consisted of a complete clinical examination and assessment of risk factors for coronary artery disease, such as smoking, excess weight, diabetes, hypertension, hypercholesterolemia and family history. The basal investigation procedure included electrocardiogram at rest and under exercise (Treadmill-test), B-mode, and Doppler echocardiography. In addition, patients with signs of cardiac ischemia were submitted to myocardial perfusion scintigraphy with ^{201}Tl and/or coronary arteri-

ography. Those who revealed valvular abnormalities or pericardial thickening with effusion also underwent cardiac catheterization for measurement of intracardiac pressures.

Statistical analysis

Time to event, defined as the cardiologic toxic effect, was calculated from the end of therapy for HD. The actuarial complication curve was calculated by the method of Kaplan and Meier.²⁴ Incidence rates were calculated by the Cutler-Ederer actuarial life-table method, using 6-month intervals.²⁵

Results

Cardiac abnormalities were diagnosed in 11 of the 102 (10.8%) patients treated with radiotherapy or with combined modality therapy and observed for 14 to 25 years. The probability

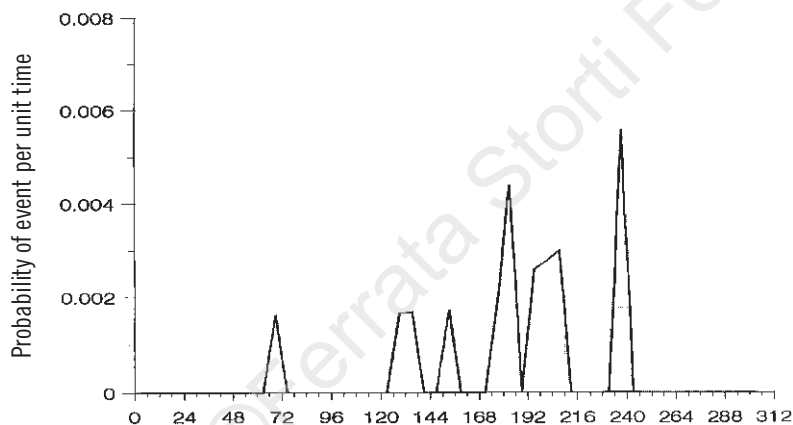


Figure 1. Incidence per 6 months of therapy-related cardiac toxicity in 102 patients.

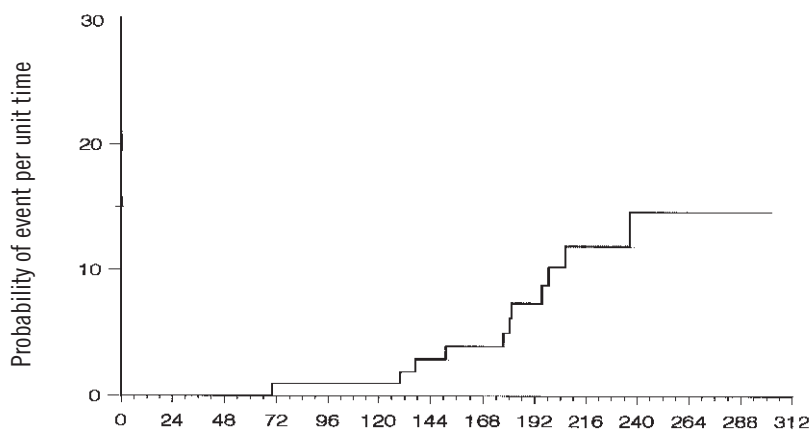


Figure 2. Cumulative actuarial risk of therapy-related cardiac toxicity in 102 patients.

of event per unit time for the whole group of patients is depicted in Figure 1. The event-density function, calculated at the midpoint of each interval (6 months) indicates that the risk of event reaches its maximum in the period between 10 and 20 years. Later, it increases to a new peak due to the decreasing number of patients at risk. The actuarial risk of cardiac toxicity is plotted in Figure 2.

Table 3 summarizes the incidence of cardiac abnormalities according to patient characteristics and treatment approaches. Seven of this group had already manifested symptoms related to these abnormalities, while 4 patients were completely asymptomatic at the time of our study. Three cases showed more than one cardiac dysfunction.

The incidence of cardiotoxic effects was 19% (3 patients) in the subset of patients treated only with radiotherapy and 9% (8 patients) in the subgroup of that received combined modality treatment (radiotherapy plus MOPP chemotherapy), respectively. These side effects were classified as constrictive or occult constrictive and coronary artery disease; three cases of con-

strictive pericarditis and 8 of coronary artery disease were observed. Three patients presented risk factors: 2 with hypercholesterolemia and 1 hypertension and smoking.

Pericarditis occurred in three (2.9%) patients; two required no treatment and one patient was given prednisone. Eight (7.9%) patients suffered from documented myocardial ischemia, 2 of whom with contemporary pericardial effusion and 1 also presented Prinzmetal's angina. Four patients had undergone coronary artery by-pass graft and two patients died from cardiogenic shock.

The cumulative incidence of cardiac complications was compared by forming three groups according to the radiation dose to the mediastinum: 36-44 Gy, 45 Gy, and 46-50 Gy. The incidence rates of cardiac disease were 0%, 10.2% and 66% in the three subsets, respectively. Because there were only 3 patients in the 46-50 Gy subset, a statistical comparison was possible between the < 45 Gy and > 45 Gy subsets: 0/21 versus 10/81 (12%) ($p=0.08$). The incidence of cardiac complications was also evaluated between patients in whom both the anterior (AP) and posterior (PA) mediastinal fields were treated daily and those in whom the two fields were irradiated on alternate days; the rates were 7.4% and 14.5% ($p=0.12$), respectively. No statistically significant differences were observed regarding age and sex.

Table 3. Cardiac toxicity (11 cases) according to patient and treatment characteristics.

Sex M/F	7/4
Histology:	
• nodular sclerosis	9/87 (10.3%)
• mixed cellularity	2/15 (13.3%)
Stage:	
• I	2/19 (10.5%)
• II	7/48 (14.5%)
• III	2/35 (5.7%)
Treatment:	
• radiotherapy alone	3/16 (19%)
• radiotherapy plus chemotherapy	8/86 (9%)
Dose:	
• < 45 Gy	0/21 (0%)
• 45 Gy	8/78 (10.2%)
• > 45 Gy	2/3 (66%)
Technique of irradiation:	
• one field per day	7/48 (14.5%)
• both opposing fields per day	4/54 (7.4%)

Discussion

Radical therapy for the cure of HD has been widely available for almost two decades. With cure has come increasing recognition of the late-appearing complications arising from treatment. While experience in the application of radiation and drug dosage has diminished the frequency of acute toxicity, cardiovascular complications of therapy remain a problem. In addition, the continued survival of patients treated 10 to 20 years ago is only now allowing us to see the late consequences of treatment. Recent evidence indicates that any part of the cardiovascular system can be subject to radiation injury. The relatively long cell-cycle time of the constituents of the cardiovascular system

apparently is the primary reason why cardiac and vascular complications of radiation often do not manifest until years after therapy.

These late sequelae consist of tissue fibrosis and necrosis. Myocardial fibrosis, constrictive pericarditis, and possibly accelerated atherosclerosis are the cardiovascular effects of late radiation reactions. This delay has become increasingly important as treatment for HD has led to long disease-free intervals. The clinician must be aware of the consequences of radiation in order to distinguish correctly between recurrent disease and radiation injury.

Pericardial diseases were the first to be recognized,^{8,9,18} and subsequent modification of irradiation techniques has decreased the amount of radiation administered to the heart in many patients. Several reports suggested that mediastinal irradiation might predispose patients to premature coronary artery disease;¹¹⁻¹³ however, convincing evidence for an increased risk of this complication is a recent development.¹⁴⁻¹⁶

The observations described in the literature list the following as risk factors: young age at irradiation, increasing duration of follow-up, total dose administered, dose rate, amount of heart volume included in the irradiated field, and concomitant chemotherapy.

Our data confirm the positive association between mediastinal irradiation and cardiac injury; we found that total irradiation dose and alternating treatment represented two important poor prognostic factors for the risk of cardiac complications. In addition, the risk increased with the increasing duration of follow-up; in fact, irradiation-induced changes are usually mild, at least during a 5-year to 10-year follow-up time, but with aging diminished diastolic compliance, for example, may lead to symptoms of heart failure. In the present study, the combined modality treatment, MOPP plus radiotherapy, did not contribute to increasing the cardiotoxic risk, unlike what was observed by others,¹⁵ probably because our patients treated with both chemotherapy and radiation received lower mediastinal doses.

The present study shows the importance of careful radiation techniques in minimizing those risks that may be necessary to maintain

excellent cure rates for HD. The best management of radiation-induced cardiac damage is prevention. First, treatment strategies have to consider the important role of new therapeutic approaches that employ new chemotherapeutic regimens associated with lower doses of limited-field irradiation, as reported in a few pediatric HD trials²⁶ and in elderly patients.²⁷⁻²⁹ Second, in order to identify the subset of asymptomatic patients, we recommend standardization of systematic screening with echocardiographic check-ups during the follow-up (every 3-4 years).

It is likely that continued refinement of therapeutic regimens based on evaluation of cardiovascular status will succeed in limiting cardiovascular toxicity without compromising anti-neoplastic activity.

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