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Asymptomatic Cardiac Disease Following Mediastinal Irradiation

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OBJECTIVES This study was designed to evaluate the potential benefit of screening previously irradiated patients with echocardiography.

BACKGROUND Mediastinal irradiation is known to cause cardiac disease. However, the prevalence of asymptomatic cardiac disease and the potential for intervention before symptom development are unknown.

METHODS We recruited 294 asymptomatic patients (mean age 42 ± 9 years, 49% men, mean mantle irradiation dose 43 ± 0.3 Gy) treated with at least 35 Gy to the mediastinum for Hodgkin's disease. After providing written consent, each patient underwent electrocardiography and transthoracic echocardiography.

RESULTS Valvular disease was common and increased with time following irradiation. Patients who had received irradiation more than 20 years before evaluation had significantly more mild or greater aortic regurgitation (60% vs. 4%, $p < 0.0001$), moderate or greater tricuspid regurgitation (4% vs. 0%, $p = 0.06$), and aortic stenosis (16% vs. 0%, $p = 0.0008$) than those who had received irradiation within 10 years. The number needed to screen to detect one candidate for endocarditis prophylaxis was 13 (95% confidence interval [CI] 7 to 44) for patients treated within 10 years and 1.6 (95% CI 1.3 to 1.9) for those treated at least 20 years ago. Compared with the Framingham Heart Study population, mildly reduced left ventricular fractional shortening (<30%) was more common (36% vs. 3%), and age- and gender-adjusted left ventricular mass was lower (90 ± 27 g/m vs. 117 g/m) in irradiated patients.

CONCLUSIONS There is a high prevalence of asymptomatic heart disease in general, and aortic valvular disease in particular, following mediastinal irradiation. Screening echocardiography should be considered for patients with a history of mediastinal irradiation. (J Am Coll Cardiol 2003; 42:743–9) © 2003 by the American College of Cardiology Foundation

Mediastinal irradiation is known to lead to symptomatic cardiac disease such as constrictive pericarditis (1), aortic and mitral valvular regurgitation (2), conduction defects (3), and coronary artery disease (4,5). Because of the high cure rate that is now possible with mediastinal irradiation, many patients with Hodgkin's disease are surviving for long periods (6) and are at risk for irradiation-induced cardiac diseases. The prevalence of preclinical cardiac disease is largely unknown and may be substantial.

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The appropriate management of asymptomatic patients with a history of mediastinal irradiation is unclear. If asymptomatic cardiac disease is common following mediastinal irradiation, then periodic screening may be beneficial if treatable conditions can be identified. For example, asymptomatic patients with valvular disease may benefit from endocarditis prophylaxis (7,8), whereas those with depressed LV dysfunction may benefit from angiotensin-converting enzyme inhibitors (9) or possibly beta-blockers (10).

To determine the potential benefit from screening asymptomatic patients following mediastinal irradiation, we addressed the following questions: What is the prevalence of asymptomatic cardiac disease following mediastinal irradiation? What patient- and treatment-related factors increase the risk of radiation-induced heart disease?

METHODS

Patient population. Patients were eligible if they had received at least 35 Gy of mantle irradiation for treatment for Hodgkin's disease, without symptomatic cardiac disease (a history of pacemaker implant [n = 1] was allowed), and gave written consent to undergo noninvasive testing with echocardiography and electrocardiography. The treatment protocol included a LV block after 15 Gy, and a subcarinal block that excluded most of the heart after 30 Gy. We identified 335 eligible subjects by attempting to contact all patients followed at Stanford Medical Center who were not known to have died or known to have symptomatic disease. Of these, 254 provided consent and were enrolled. An additional 40 eligible patients treated elsewhere but meeting

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Abbreviations and Acronyms

HF = heart failure
LV = left ventricular
MI = myocardial infarction

study criteria were included. Enrollment lasted from October 1994 through November 1998. The study protocol was approved by the Human Research Committee at Stanford University Medical Center.

Study protocol: noninvasive evaluation. AUSCULTATION AND ELECTROCARDIOGRAPHY. Each patient underwent resting 12-lead electrocardiography. Abnormalities in conduction, QRS and ST complexes and the presence of LV hypertrophy were defined using Minnesota criteria (11).

A subset of 242 patients underwent cardiac auscultation by their attending medical or radiation oncologist, who was blind to the results of echocardiography. A group of 212 was examined on the day of enrollment, and another 30 were examined during the preceding 30 days. The presence of a murmur and timing (systolic vs. diastolic) were recorded. There was no significant difference in age, gender, dose of radiation, or underlying valvular disease between those undergoing and those not undergoing auscultation.

ECHOCARDIOGRAPHY. Each subject underwent two-dimensional echocardiography, M-mode echocardiography, color and pulsed Doppler studies of the aortic, mitral, tricuspid, and pulmonary valves. All studies were performed using commercially available ultrasound scanners (HP Sonos 1500, 2500, Hewlett Packard, Mountain View, California), and were recorded on 1/2-inch super VHS videotape. Standard parasternal long-axis, short-axis, apical four-chamber, and subcostal two-dimensional views were obtained. M-mode measurements were obtained according to the recommendations of the American Society of Echocardiography (12). Cardiac volume measurements (from M-mode) were standardized to height. Left ventricular mass was calculated using the modified formula of Devereux (13).

Regurgitation was assessed visually using definitions similar to the Framingham Heart Study (14). Mitral and tricuspid valvular regurgitation were graded using the ratio of the color Doppler-jet area to the atrial area as a guide (>40% as severe, 20% to 40% as moderate, <20% but extending at least 1 cm into the atrium as mild, and extension <1 cm as trace). Regurgitation leading to reversal in the hepatic or pulmonary veins was also considered severe. Aortic and pulmonic regurgitation were visually graded using the ratio of the width of the color jet to the diameter of the outflow tract (>50% as severe, 25% to 50% as moderate, 10% to 24% as mild, and <10% as trace). Aortic stenosis was considered present if the motion of the aortic valve leaflets were restricted and the peak aortic velocity was more than 2.0 m/s. Pericardial thickening and regional wall motion abnormalities were graded using standard criteria (15,16). The echocardiographic studies were interpreted by a single experienced echocardiographer who was aware that the patient had received mediastinal irradiation but was blind to the details of irradiation and to other study data. The Food and Drug Administration's classification of valve disease was used to classify lesions into significant (mild or greater aortic regurgitation, moderate or greater mitral or tricuspid regurgitation, aortic stenosis) and nonsignificant pathology (7). To directly compare our population from published population values from the Framingham Heart Study, we also classified valvular lesions as trace, mild, and moderate or severe.

When available, we used published reports from the Framingham Heart Study as a measure of the prevalence of echocardiographic and electrocardiographic disease in the general population. For Framingham data that were age- and gender-specific, we adjusted the summary Framingham value to match the age and gender distribution of our population.

OUTCOME. We contacted patients at yearly intervals to determine death or nonfatal cardiac events or new cardiac diagnoses. Cardiac outcomes included a new diagnosis of heart failure (HF), constrictive pericarditis, symptomatic valvular disease, coronary artery disease (revascularization, myocardial infarction [MI], unstable angina, stable angina), and syncope.

STATISTICS. Patients were grouped based on the number of years between irradiation and examination (2 to 10, 11 to 20 and >20) because initial analysis revealed a strong association between time following irradiation and prevalence of cardiac disease. Descriptive data are given as percentages or means ± SD. Comparisons of means were performed using Student *t* test and analysis of variance. Differences in proportions were performed using the chi-square test. Multivariate analysis was performed using standard least-squares regression if the dependent variable was continuous, logistic regression if the dependent variable was categorical, and proportional hazards if the outcome was event-free survival. Multivariate models initially included the following independent variables: age, gender, hypertension (yes/no), diabetes (yes/no), chemotherapy (yes/no), biologically equivalent irradiation dose (17), and time following irradiation. Variables were removed from the model stepwise until only those variables significantly associated ($p < 0.05$) with the dependent variable remained. Survival curves were determined using Kaplan-Meier analysis. Differences between survival curves were evaluated using the log-rank statistic. All analyses were performed using JMP (SAS Institute, Cary, North Carolina) statistical software. A two-tailed p value <0.05 was considered statistically significant.

Table 1. Patient Characteristics

Characteristic	Value
Number	294
Age (yrs)	42 ± 9
Male gender (%)	49
Hypertension (%)	9
Diabetes (%)	1
Thyroid replacement (%)	56
Time following irradiation (yrs)	15.0 ± 7
Mean mantle irradiation dose (Gy)	43 ± 0.3
Mean biologic equivalent dose*	71 ± 7
Treatment with chemotherapy (%)	56

*For calculation of the biological equivalent dose (30).

RESULTS

The characteristics of the enrolled patients are listed in Table 1. There were no significant differences in mean age and gender distribution between the locally treated (n = 254) and referral populations (n = 40); however, the referral population had received slightly less mantle irradiation (42 vs. 44 Gy, p = 0.02). The patients ranged in age from 21 to 75 years and approximately half were men. A majority of patients (59%) received 44 mantle Gy (range 35 to 70). Time from irradiation to examination varied from 2 to 33 years.

Valvular disease. Valvular disease was several-fold more common in irradiated patients than in the Framingham population (14,18,19) (Table 2). This finding was most striking for aortic regurgitation (Fig. 1), where the age- and gender-adjusted risk was sevenfold higher for any aortic regurgitation and 34-fold higher for moderate or greater aortic regurgitation compared with the Framingham population. Significant valve disease for which endocarditis prophylaxis should be considered (mild or greater aortic regurgitation, moderate or greater mitral or tricuspid regurgitation, aortic stenosis) was noted in 29% of irradiated patients compared with 3% for an age- and gender-matched Framingham cohort (14). The number needed to screen with echocardiography to identify a candidate for endocarditis prophylaxis decreased dramatically with time following irradiation: 13 (95% confidence interval [CI] 7 to 44) for patients at 2 to 10 years, four (3 to 6) for those at 11 to 20 years and 1.6 (1.3 to 1.9) for those more than 20 years following irradiation.

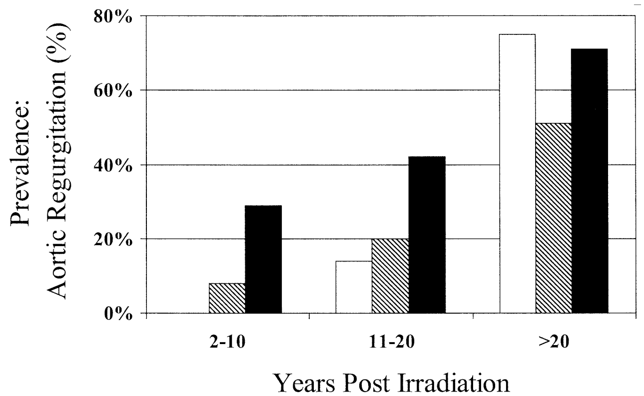

Figure 1. Prevalence of mild or greater aortic regurgitation stratified by age and time following irradiation. The prevalence of aortic regurgitation increases markedly with both age and time following irradiation. **Open bars** = age <40 years; **lined bars** = age 40 to 50 years; **solid bars** = age >50 years.

The degree of valvular disease (thickening and regurgitation) was related to time following irradiation (latency period) for all valves, although the increase in disease over time was greatest for the aortic valve (Table 2). For patients irradiated within the past 10 years the prevalence of aortic (13%) and mitral thickening (28%) was significantly less ($p < 0.0001$) than for those with irradiation more than 20 years before evaluation (aortic 61%, mitral 66%). The

Table 2. Valvular Disease Following Irradiation

	Years Following Irradiation					General Population†	
Echocardiographic Finding	All Patients n = 294	2–10 n = 89	11–20 n = 132	>20 n = 73	p Value*	Prevalence (%)	Source
Aortic regurgitation							
Trace (%)	27 (9)	9 (10)	13 (10)	5 (7)	0.71	3.1	(14)
Mild (%)	62 (21)	3 (3.4)	26 (20)	33 (45)	< 0.0001	1.3	(14)
Moderate or severe (%)	15 (5.1)	1 (1.1)	3 (2.3)	11 (15)	< 0.0001	0.15	(14)
Mitral regurgitation							
Trace (%)	87 (30)	27 (30)	44 (33)	16 (22)	0.21	75	(14)
Mild (%)	105 (36)	21 (24)	49 (37)	35 (48)	0.005	13	(14)
Moderate or severe (%)	10 (3.4)	2 (2.3)	5 (3.8)	3 (4.1)	0.71	0.54	(14)
Tricuspid regurgitation							
Trace (%)	86 (29)	25 (28)	43 (33)	18 (25)	0.47	70	(14)
Mild (%)	43 (15)	8 (9)	19 (14)	16 (22)	0.07	13	(14)
Moderate or severe (%)	4 (1.4)	0 (0)	1 (0.8)	3 (4.1)	0.06	0.55	(14)
Pulmonic regurgitation‡							
Trace (%)	106 (36)	37 (42)	45 (34)	24 (33)	0.40	17	(32)
Mild (%)	20 (7)	2 (2)	9 (7)	9 (12)	0.04	< 0.5	(32)
Moderate or severe (%)	0 (0)	0 (0)	0 (0)	0 (0)	1.0	< 0.5	(32)
Aortic stenosis (%)	13 (4)	0 (0)	1 (1)	12 (16)	0.008	< 0.5	(33)

*p for differences across groups based on time following irradiation. Percentages may not add up to 100 due to rounding; †Framingham data adjusted for age and gender to match the irradiated cohort; ‡Pulmonic regurgitation could not be measured in two patients (group 2–10 years and group 11–20 years) due to poor image quality.

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Table 3. LV Size and Function Following Irradiation

LV Measurement	Years Following Irradiation: All Patients (n = 263)	2–10 (n = 84)	11–20 (n = 120)	>20 (n = 59)	p Value†	General Population*: Values	Reference
Fractional shortening (%)	31 ± 6	32 ± 5	31 ± 5	31 ± 6	0.74	36 ± 4	(25)
Fractional shortening < 30% (%)	95 (36)	32 (38)	39 (33)	24 (41)	0.51	3	(18)
Mass/height (g/m)‡	90 ± 27	93 ± 26	89 ± 26	91 ± 30	0.59	117	(19)
Wall thickness (posterior + septal, cm)	1.9 ± 0.3	1.9 ± 0.3	1.9 ± 0.3	1.9 ± 0.4	0.88	1.9 ± 0.2	(25)
End diastolic dimension (cm)	4.6 ± 0.5	4.7 ± 0.5	4.6 ± 0.5	4.5 ± 0.5	0.24	5.1 ± 0.4	(25)
End systolic dimension (cm)	3.2 ± 0.4	3.2 ± 0.5	3.2 ± 0.4	3.1 ± 0.5	0.71	3.3 ± 0.3	(25)

*Framingham data; †p for differences across groups based on time following irradiation; ‡LV mass/height available for 225 patients (latency 2–10 years, 78; latency 11–20 years, 111; latency >20 years, 36).
LV = left ventricular.

prevalence of aortic stenosis also increased with the increasing latency period (Table 2). After adjusting for age and gender, the odds of having aortic stenosis increased 13.9-fold (95% CI 12.2 to 15.8) for each 10-year increase in latency period.

Older age and female gender were associated ($p < 0.05$) with greater aortic valve regurgitation, but not with mitral, tricuspid, or pulmonic regurgitation after adjustment for the latency period. No patient <40 years and a latency period of 10 years or less had mild or greater aortic regurgitation (Fig. 1). In contrast, 71% (17/24) patients >50 years with a latency period >20 years had at least mild aortic regurgitation. After adjustment for age and latency period, women had 2.1 (95% CI 1.5 to 3.0)-fold greater odds of having aortic regurgitation than men.

Calcification of the aortic-mitral intervalvular fibrosa. There was an unusually marked calcification of the intervalvular fibrosa of the aortic valve and the anterior mitral valve leaflet in 26% (76/294) patients. This calcification was isolated (without associated aortic or mitral valve thickening) in 8% (23/294). Calcification of the aortic valve, mitral valve, or the intervalvular fibrosa was present in 90% (66/73) of patients treated >20 years earlier, compared with 39% (14/36) for those treated within five years of echocardiography.

Auscultation and valvular disease. Aortic regurgitation was rarely suspected on the basis of the physical examination of the patient's attending physician (noncardiologist). Of 64 patients potentially at risk for endocarditis from aortic regurgitation (mild or greater) undergoing auscultation, a diastolic murmur was detected in only four patients (6.3%).

Systolic murmurs were heard in 71 (29%) of the 243 patients that underwent auscultation. Of 11 patients with moderate or greater mitral or tricuspid regurgitation, a systolic murmur was heard in eight patients (73%), compared with 62 of 232 (27%) patients with less or no regurgitation ($p = 0.002$). Overall the systolic murmur had a sensitivity of 80% (16/20) but a limited specificity of 77% (168/223) with a positive predictive value of only 23% (16/71) for detecting significant valve disease that is typically associated with a systolic murmur (aortic stenosis, moderate mitral, or moderate tricuspid regurgitation).

LV disease. M-mode tracings were adequate for measurement of LV dimensions in 263 (89%) patients (Table 3). Depressed fractional shortening (<30%) was more frequent in patients following irradiation (36%) than in a Framingham cohort without a history of MI (3%, $p < 0.01$) (20). In multivariate analyses only age was independently associated with fractional shortening (absolute 0.15% increase in fractional shortening per year, $p < 0.0001$).

Regional wall motion abnormalities were also more common in our cohort than in the Framingham population. Compared to the 5% prevalence in Framingham, the prevalence of wall motion abnormalities was 13% (12/89) for those with a latency period of two to 10 years, 18% (24/132) for a latency period of 11 to 20 years, and 29% (21/73) for a latency period more than 20 years ($p = 0.04$ for difference between latency groups). Only one segment in one patient was considered akinetic. There were no dyskinetic segments identified. In multivariate analyses regional wall motion abnormalities were independently related to a greater biologically equivalent dose (odds ratio 1.07 per one-unit increase, 95% CI 1.02 to 1.13), and older age (odds ratio 1.7 per 10-year increase, 95% CI 1.2 to 2.4) in addition to time following irradiation.

LV mass. Left ventricular mass was lower for irradiated patients than for the Framingham population (Table 3). Left ventricular hypertrophy (defined as more than 163 g/m for men and 121 g/m for women) was present in 6% (7/121) of female and 2% (2/104) of male patients compared with 19% of women and 16% of men in the Framingham Heart Study (21). The difference in mass was due to smaller LV diastolic volume in patients following irradiation, as systolic volume and wall thickness were similar to the Framingham cohort.

We found that ventricular mass adjusted for height remained constant or decreased slightly over time following irradiation. This is opposite to the usual increase in LV mass that occurs with aging (22). Although mass was not clearly related to the latency period in univariate analysis (Table 3), when we stratified by age a clear trend toward lower mass with greater latency period was observed (Fig. 2). In multivariate analysis that controlled for gender, ventricular mass decreased by 0.6 g/m ($p = 0.001$) for each year

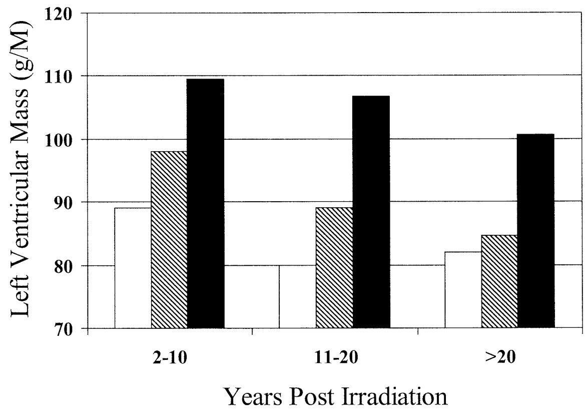

Figure 2. Mean left ventricular mass adjusted for body height and stratified by age and time following irradiation. As previously described for the general population, left ventricular mass increases with age. However, for any age group, mass decreases as time following irradiation increases. **Open bars** = age <40 years; **lined bars** = age 40 to 50 years; **solid bars** = age >50 years.

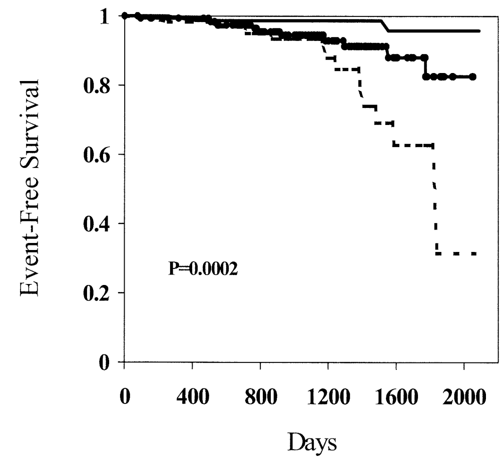

Figure 3. Survival free from cardiac events (death, heart failure, symptomatic coronary artery disease, valve replacement) is displayed for patients grouped by time following irradiation. The event rate increases with increasing time following irradiation, which persists after adjustment for age, gender, and radiation dose. **Solid line** = 2 to 10 years; **line with circles** = 11 to 20 years; **dashed line** = >20 years.

following irradiation, but increased by 0.8 g/m ($p < 0.0001$) for each year increase of age. Similar findings were observed for combined septal and posterior wall thickness, which decreased by 0.05 mm ($p = 0.08$) for each year following irradiation, but increased by 0.1 mm ($p < 0.001$) for each year increase in age.

Pericardial disease. Pericardial thickening was present in 21% (62/294) of patients compared with a Framingham prevalence of 2.5% (23). Pericardial effusions (all small) were noted in 10 (3%). Pericardial thickening was slightly more common in patients with long latency periods with a prevalence of 16% (14/89) for the 2 to 10 year latency group, 18% (24/132) for the 11 to 20 year latency group, and 33% (24/73) for the >20-year latency group ($p = 0.02$). No patient had wall-motion abnormalities or Doppler findings suggestive of constrictive pericarditis (>25% variation in E velocity with respiration and deceleration time 160 ms or less).

Electrocardiographic findings. Electrocardiography (98% had adequate tracings) was rarely abnormal, and prevalence rates were similar to Framingham reports (24–27) (Table 4). The prevalence of LV hypertrophy, right bundle branch block, and abnormal Q-waves increased with increasing time following irradiation. Resting heart rate also was higher in patients with longer latency periods (70 ± 13 beats/min for ≤10 years, 74 ± 12 for 11 to 20 years, and 81 ± 10 for >20 years, $p < 0.0001$). In multivariate analyses controlling for age, gender, diabetes, hypertension, and dose of irradiation, a 10-year increase in latency period was independently predictive of a higher resting heart rate (increase 3.7 beats/min, 95% CI 1.3 to 6.1), right bundle branch block (odds ratio 7.3, 95% CI 1.2 to 45), and abnormal Q-waves (odds ratio 4.9, 95% CI 1.7 to 14).

Follow-up. During 3.2 ± 1.3 years of follow-up nine patients died (one MI, four malignancy, two pulmonary disease, one renal failure, one unknown). Another 16 patients developed new cardiac disease (five angina or revascularization, five nonfatal MI, three HF, two constrictive pericarditis, one syncope). Event-free survival was strongly associated with time from irradiation to echocardiography (Fig. 3). Using a proportional hazards model that controlled for age, gender, radiation dose, patient characteristics, and echocardiographic findings, only the latency period (time from irradiation to echocardiography) was independently associated with worse event-free survival (hazard ratio 3.6 per 10-year increase in latency period, 95% CI 1.8 to 7.4).

Table 4. Electrocardiogram Findings Following Irradiation

	Years Following Irradiation					General Population*	
Electrocardiographic Finding	All Patients n = 288	2–10 n = 87	11–20 n = 130	>20 n = 71	p Value†	Values (%)	Reference
1st degree AV block (%)	2 (0.7)	1 (1)	1 (0.8)	0 (0)	0.68	1.4	(34)
Right bundle branch block (%)	8 (3)	0 (0)	2 (2)	6 (8)	0.003	0.7	(35)
Left bundle branch block (%)	1 (0.4)	0 (0)	0 (0)	1 (1)	0.25	0.3	(35)
LV hypertrophy (%)	6 (2)	0 (0)	2 (2)	4 (6)	0.03	1.9	(36)
Abnormal Q waves (%)	11 (4)	0 (0)	4 (3)	7 (10)	0.005	1.4	(34)
ST or T-wave abnormalities (%)	15 (5)	4 (5)	6 (5)	5 (7)	0.74	4	(37)

*Population data from Framingham, Massachusetts or Tecumseh, Michigan; †p for differences across groups based on time following irradiation.
AV = atrioventricular; LV = left ventricular.

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DISCUSSION

This study documented frequent abnormalities in valvular function, LV mass, and systolic function in asymptomatic patients that had previously received mediastinal irradiation. The prevalence of cardiac disease was several-fold higher than in the Framingham population and increased with time following irradiation. Previous studies have shown that symptomatic disease occurs in approximately 5% of patients by 10 years following treatment for Hodgkin's disease (28,29). The results of this study show that by 20 years the majority of asymptomatic patients have valvular disease for which endocarditis prophylaxis has been recommended.

Abnormalities of the aortic valve were more common than abnormalities of the mitral and tricuspid valves although all were more frequently incompetent than in the Framingham population. The increased frequency of aortic valve pathology is likely due to the proximity of the aortic valve to the mediastinal radiation field. By 20 years following irradiation few patients had a normally functioning aortic valve.

An important result from this study is that many irradiation induced abnormalities become more frequent over time, a finding that was independent of age. Irradiation appears to initiate a degenerative process that continues for at least the next 20 years. Thus, the absence of valvular disease early after irradiation does not indicate a low risk for valvular disease in the future.

Our study observed a progressive decrease in LV mass, diastolic cavity dimensions, and wall thickness following irradiation after adjustment for age. Although radiation-induced atrophy of noncardiac muscle has been documented (30), the finding of decreasing LV mass with time following irradiation has not been previously reported and is opposite to the normal increase with age (22). Left ventricular systolic dimensions were similar to the Framingham population (31) resulting in a mildly reduced fractional shortening in the irradiated patients. The clinical implications of reduced LV mass and fractional shortening are unclear and further follow-up is needed to determine if these patients are at increased risk for HF or other cardiac disease.

Comparison with previous studies. Several prior studies have evaluated patients with Hodgkin's following irradiation with two-dimensional (28,29,32) or M-mode echocardiography (33). These studies included symptomatic patents, were smaller than the present investigation (sample size range 25 to 116), and had a shorter time from treatment to evaluation (range 5 to 11 years) compared with our study. Our study is consistent with these reports in noting a high prevalence of aortic valvular disease. Our finding of decreased cavity size and reduced LV systolic function following irradiation confirms the findings of an early study (33) but contradicts a more recent investigation (34) showing no effect of irradiation on systolic function.

Clinical implications. Our study has several clinical implications. Endocarditis prophylaxis would be recommended for 29% of patients using the criteria from the Food and Drug Administration (7). Screening with echocardiography may thus be beneficial, particularly in those that have survived 10 years following irradiation, where one in four patients are candidates for endocarditis prophylaxis. The physical exam (by the attending radiation or medical oncologist) provided limited information, with a positive predictive value of 25% for a systolic murmur to detect aortic stenosis, moderate mitral or tricuspid regurgitation, and a sensitivity of 5% for a diastolic murmur to detect mild or greater aortic regurgitation. Pending a cost-effectiveness analysis, it appears reasonable to perform at least one screening echocardiogram in patients who have survived 10 years following mediastinal irradiation (35 Gy or more).

Study limitations. This study has several limitations. Irradiation treatment has changed over the past 30 years with a gradual decrease in the total dose used. Previously, patients received more than 40 Gy regardless of the use of chemotherapy. During the past 10 to 15 years patients treated with radiation alone frequently receive 44 Gy, whereas those treated with eight weeks of chemotherapy may receive 30 Gy if they have early disease. The average follow-up after echocardiography was less than four years in our study. Therefore, the rate of progression from asymptomatic to symptomatic disease is unclear. Our study was limited to patients with a prior history of Hodgkin's disease. However, other studies have documented an increased risk of cardiac disease following radiation treatment for testicular (35) and breast cancer (36).

Conclusions. In summary, our study found a high prevalence of cardiac abnormalities in asymptomatic patients following mediastinal irradiation. In particular, aortic valve disease, reduced LV systolic function, and pericardial disease were noted more frequently in our irradiated cohort than in the Framingham population. In contrast, LV mass was reduced compared to Framingham subjects. The latency period following irradiation was the most important risk factor for development of valvular and conduction disease abnormalities and was independent of age. These findings suggest that echocardiography should be considered during follow-up care for asymptomatic patients who have received more than 35 Gy of mediastinal irradiation.

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