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ORIGINAL REPORT

Screening for Coronary Artery Disease After Mediastinal Irradiation for Hodgkin's Disease

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ABSTRACT

Purpose
Incidental cardiac irradiation during treatment of thoracic neoplasms has increased risks for subsequent acute myocardial infarction or sudden cardiac death. Identifying patients who have a high risk for a coronary event may decrease morbidity and mortality. The objective of this study was to evaluate whether stress imaging can identify severe, unsuspected coronary stenoses in patients who had prior mediastinal irradiation for Hodgkin's disease.

Patients and Methods
We enrolled 294 outpatients observed at a tertiary care cancer treatment center after mediastinal irradiation doses ≥ 35 Gy for Hodgkin's disease who had no known ischemic cardiac disease. Patients underwent stress echocardiography and radionuclide perfusion imaging at one stress session. Coronary angiography was performed at the discretion of the physician.

Results
Among the 294 participants, 63 (21.4%) had abnormal ventricular images at rest, suggesting prior myocardial injury. During stress testing, 42 patients (14%) developed perfusion defects (n = 26), impaired wall motion (n = 8), or both abnormalities (n = 8). Coronary angiography showed stenosis ≥ 50% in 22 patients (55%), less than 50% in nine patients (22.5%), and no stenosis in nine patients (22.5%). Screening led to bypass graft surgery in seven patients. Twenty-three patients developed coronary events during a median of 6.5 years of follow-up, with 10 acute myocardial infarctions (two fatal).

Conclusion
Stress-induced signs of ischemia and significant coronary artery disease are highly prevalent after mediastinal irradiation in young patients. Stress testing identifies asymptomatic individuals at high risk for acute myocardial infarction or sudden cardiac death.

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INTRODUCTION

Mediastinal irradiation has contributed to cure and improved survival in Hodgkin's disease and other mediastinal neoplasms.[1-9] However, incidental irradiation of the heart during the treatment of mediastinal tumors has been associated with increased risks for subsequent death from ischemic and other heart diseases.[10-25] Radiation of the left breast or chest wall during breast cancer therapy using techniques that included underlying myocardium also increased risks for death due to cardiac disease.[26-32] Because of prolonged survival after treatment of these malignancies, substantial populations of patients are at risk for radiation-induced coronary artery disease, acute myocardial infarction, or sudden cardiac death. Many irradiated patients who died suddenly as a result of acute myocardial infarction lacked conventional risk factors for coronary artery disease and reported no symptoms of coronary disease during clinical evaluations shortly before a fatal event.[15] If patients with severe coronary artery disease could be identified, their survival might improve with revascularization or other interventions.[33] We prospectively performed stress echocardiography and nuclear scintigraphy to determine whether these screening tests could identify individuals with unsuspected, severe coronary disease, and to estimate the prevalence of significant coronary disease after the moderately high doses of irradiation used to treat Hodgkin's disease.

PATIENTS AND METHODS

Patient Population

The study included Hodgkin's disease patients who received ≥ 35 Gy to the mediastinum because prior analyses identified an excess risk for death from myocardial infarction confined to those who received higher radiation doses.[15] These criteria identified 972 patients from a computerized database of 2,294 patients treated for Hodgkin's disease at Stanford University between 1960 and 1995. In this cohort, 345 patients were known to have died. Their causes of death were established by review of clinical records, autopsy or coroner's reports, death certificates, and information from physicians or family members. Six hundred twenty-seven patients were alive at last contact. We contacted 473 (75%) of these patients during routine appointments or by mail regarding participation in a cardiac screening study. We offered to screen patients after informing them about health risks identified in survivors of Hodgkin's disease. We excluded from screening patients who reported a history of coronary artery disease or cardiac interventions, and confirmed their cardiac diagnoses from discharge summaries or procedure reports. Patients were enrolled from October 1994 through November 1998. The Human Subjects Committee at Stanford University Medical Center (Stanford, CA) reviewed and approved the study annually.

Study Protocol

All patients had fractionated serum cholesterol testing, a resting ECG, and a stress echocardiogram. Echocardiograms were performed using commercially available ultrasound scanners (HP Sonos 1500 and 2500; Hewlett Packard, Mountain View, CA), and were recorded on 0.5-in. super video casette recorder tape. Standard parasternal long axis, short axis, and apical four-chamber images were obtained before and after cardiac stress. After baseline echocardiography, 97% of subjects underwent treadmill testing using a Bruce protocol that limited exercise duration by symptoms. Patients who reported impaired walking ability or medications that blocked beta-adrenergic activity (3%) underwent dobutamine cardiac stress using a standardized protocol.[16] Standard treadmill or dobutamine stress protocols and imaging techniques were used.[34] ECG abnormalities were quantified using the Duke Treadmill Score.[35] Myocardial perfusion imaging was performed during the same stress session starting with the 16th patient. Approximately 2 minutes before peak stress, a radioactive tracer (technetium-99m–labeled tetrofosmin, 12 to 25 mCi) was injected intravenously. Echocardiography was repeated immediately after peak stress. Single-photon emission computed tomography scans of radionuclide distribution during stress were obtained within 60 minutes of injection after completion of the stress echocardiogram. Rest imaging was performed with 3.5 mCi of thallium-201 either before the exercise test or on the day after exercise testing.

Any stress-induced wall motion abnormality, stress-induced perfusion defect, or horizontal or down-sloping ST depression $\geq$ 1 mm on ECG tracings was considered a positive test for ischemia. Patients with a positive stress test were advised to undergo coronary angiography but performance of the procedure was at the discretion of the patient's physician. The results of coronary angiography performed after screening without an intervening event were used to determine the predictive value of noninvasive imaging.

Statistical Analyses

Descriptive data are given as percentages or means $\pm$ standard deviation. Differences in mean values were evaluated using the *t* test and analysis of variance. Differences in proportions were evaluated using the χ^2 test. To estimate radiation dose intensity, biologically effective dose (BED) was calculated from each patient's mediastinal radiation doses using the formula described by Fowler and an estimated α/β ratio of 3 for a late-reacting tissue.[36] The volume of myocardium irradiated varied according to radiation blocking techniques, use of chemotherapy before irradiation, and the proximity of mediastinal Hodgkin's disease. This could not be quantified usefully from available records. Relative and absolute risks for heart disease were calculated using the subject-year method, with general population rates from the United States Decennial Life Tables.[37,38] Multivariate analysis was performed using standard least-squares regression if the dependent variable was continuous or logistic regression if the dependent variable was categoric. Multivariate models initially included the following independent variables: age, sex, hypertension (yes/no), diabetes (yes/no), low-density lipoprotein and high-density lipoprotein cholesterol, smoking history (yes/no), chemotherapy (yes/no), irradiation dose in BED, and time after irradiation. Variables were removed from the model sequentially, until only those variables that were predictors ($P < .05$) of the dependent variable remained. All analyses were performed using JMP statistical software (SAS institute, Cary, NC). A two-tailed $P < .05$ was considered statistically significant.

RESULTS

Prior Coronary Disease and Patients Excluded From Screening

Among the 473 patients evaluated for study, 42 (9%) reported a history of established coronary artery disease with prior myocardial infarction (n = 12), coronary artery bypass graft surgery (n = 16), percutaneous transluminal angioplasty (n = 4), or coronary stenosis verified by angiography and managed medically (n = 10). Seven others reported a history of valvular heart surgery (n = 3), prior pericardiectomy for constrictive pericarditis (n = 1), or congestive heart failure without documented coronary artery disease (n = 3) and did not undergo screening. Of the remaining 424 patients, 308 (73%) agreed to participate and completed testing. Fourteen patients were excluded after testing for mediastinal radiation doses less than 35 Gy (n = 11) or identification of a non-Hodgkin's lymphoma histology (n = 3) on review of records.

Study Patients

Characteristics of the 294 participants are summarized in Table 1 according to the time interval after irradiation. The patients were irradiated between 1964 and 1994 (median, 1982) with 35.0 to 54.6 Gy to the mediastinum (minimum, 35 Gy; 25%, 43.2 Gy; median, 44 Gy; 75%, 44.5 Gy; maximum, 54.6 Gy). At the time of testing, patients irradiated earlier were older, had slightly higher total cholesterol levels, received higher radiation doses to the mediastinum at a higher dose per fraction, and received chemotherapy less often than patients treated more recently. Standard risk factors for coronary artery disease including diabetes, hypertension, elevated low-density lipoprotein cholesterol, reduced high-density lipoprotein cholesterol, and smoking were uncommon.

Exercise Testing

All 294 patients underwent stress echocardiography (97% exercise, 3% dobutamine), and 292 (99%) had interpretable images at stress and rest. In 274 patients radionuclide perfusion imaging was performed at the same stress session and was interpretable in all patients. The stress ECG was interpretable in 282 patients. Table 2 lists the results of exercise testing. Signs of possible stress-induced ischemia (ST change, wall motion, or perfusion abnormality) were identified in 18.4% of patients (54 of 294). Stress-induced perfusion abnormalities were more common (12%) than stress-induced wall motion abnormalities (5%) or changes in the ST segment on the ECG (7%). In resting studies, 46 patients had abnormal wall motion, seven had radionuclide perfusion defects, and 10 had corresponding abnormalities on both studies. Exercise-induced changes suggesting ischemia were seen in 15 of those with segmental resting wall motion abnormalities (33%), five of those with resting perfusion defects (71%), and five of those with abnormalities on both resting studies (50%).

Coronary Angiography

Based on the imaging results, 40 patients (14%) underwent coronary angiography (Tables 3 and 4). This included 90% (38 of 42) of all patients with abnormal stress echocardiography or perfusion imaging, and two patients who reported exertional dyspnea and had

Table 1. Patient Characteristics at the Time of Stress Testing

Characteristic	All Patients (N = 294)	Years After Irradiation: 2-10 (n = 89)	11-20 (n = 132)	> 20 (n = 73)	*P*
Age, years					< .0001
Mean	42	37	43	46	
SD	9	9	9	7	
Male	49%	47%	47%	56%	.40
Time after radiation, years					< .0001
Mean	15	6	15	25	
SD	7	3	3	3	
Mean mediastinal radiation dose, Gy					< .0001
Mean	43.5	41.0	44.9	44.1	
SD	3.4	3.6	2.8	2.3	
Biological equivalent radiation dose, units*					< .0001
Mean	70.8	64.0	72.8	75.5	
SD	7.1	6.2	5.1	5.0	
Treatment with chemotherapy	56%	66%	54%	46%	.07
Hypertension	9%	7%	9%	13%	.47
History of smoking	27%	17%	29%	35%	.04
Diabetes mellitus	1.0%	1.1%	0.8%	1.4%	.91
Total cholesterol, SI					.003
Mean	5.2	4.9	5.2	5.6	
SD	1.5	0.9	0.9	2.4	
HDL cholesterol < 0.9 SI (35 mg/dL)	9%	8%	11%	7%	.61
LDL cholesterol > 4.1 SI (160 mg/dL)	10%	7%	11%	14%	.34

Abbreviations: SD, standard deviation; SI, International System of Units; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
*For calculation of the biological equivalent dose, see Fowler.[36]

abnormal wall motion and perfusion at rest. Twelve patients with ST segment change during exercise (1.0 to 2.0 mm) without symptoms or signs suggesting ischemia on imaging were not advised to undergo coronary angiography.

Coronary artery stenosis exceeded 50% in 22 patients (7.4% of screened patients; 55% of those examined with angiography), and narrowing exceeded 70% in 16 of these. Eight patients (2.7% of screened patients) had severe coronary disease with ≥ 50% stenosis of

Table 2. Stress Testing Results

Result	All Patients No.	All Patients %	2-10 No.	2-10 %	11-20 No.	11-20 %	> 20 No.	> 20 %	*P*
Exercise time, Bruce protocol, minutes*									.05
Mean	9.9		10.4		9.8		9.4		
SD	2.5		2.5		2.5		2.5		
Duke Treadmill Score*									.03
Mean	9.3		10.2		9.0		9.0		
SD	3.2		3.0		3.2		3.1		
Resting wall motion abnormality	56 of 293	19	12 of 89	13	23 of 132	17	21 of 72	29	.04
Mild hypokinesis	39		8		18		13		
Moderate hypokinesis	12		4		4		4		
Severe hypokinesis/akinesis	5		0		1		4		
Fixed perfusion defect	17 of 274	6	4 of 83	5	6 of 122	5	7 of 69	10	.30
Stress induced wall motion abnormality	16 of 292	5	1 of 89	1	9 of 132	7	6 of 71	8	.05
Stress induced perfusion abnormality	32 of 274	12	4 of 83	5	14 of 122	11	14 of 69	20	.01
Stress induced ECG changes	20 of 282	8	3 of 85	5	12 of 128	10	5 of 69	7	.34
Coronary angiography performed†	40 of 294	14	5 of 89	6	19 of 132	14	16 of 73	22	.02

Abbreviation: SD, standard deviation.
*Sample size for exercise time and Duke Treadmill Score: years after irradiation, 2-10 (n = 62); 11-20 (n = 110); > 20 (n = 55).
†After stress testing but prior to a cardiac event. Includes one patient with acute myocardial infarction diagnosed at the time of angiography (coronary thrombus, with new Q waves on the electrocardiogram).

Table 3. Angiography Results

Result	All Patients (n = 40)		Years After Irradiation 2-10 (n = 5)		11-20 (n = 19)		> 20 (n = 16)	
	No.	%	No.	%	No.	%	No.	%
Coronary disease ≥ 50%	22	55	2	40	11	58	9	56
Coronary disease ≥ 70%	16	40	1	20	9	47	6	38
Left main or three-vessel disease	8	20	0	0	6	32	2	13
Two-vessel disease	4	10	0	0	2	11	2	13
One-vessel disease	4	10	1	20	1	5	2	13
Left coronary ostial disease ≥ 50%	6	15	0	0	4	21	2	13
Right coronary ostial disease ≥ 50%	5	13	1	20	2	10	2	13
PTCA after screening angiogram	1	3	1	20	0	0	0	0
CABG after screening angiogram	8	20	0	0	7	37	1	6

NOTE. There are no significant differences ($P > .15$) between groups for all comparisons.
Abbreviations: PTCA, percutaneous transluminal coronary angioplasty with or without stenting; CABG, coronary artery bypass grafting.
*Includes two patients who had negative screening exercise tests but abnormal resting echocardiography.

the left main coronary artery or three-vessel coronary artery disease with at least one stenosis ≥ 70%. Seven patients had one- or two-vessel disease. One of these patients underwent immediate angioplasty with stent placement. Seven patients underwent coronary artery bypass grafting solely on the basis of screening. An eighth patient underwent bypass grafting for two-vessel coronary disease and an unreported acute myocardial infarction after screening that was diagnosed during coronary angiography. Eighteen patients (45%) with abnormal stress tests had less than 50% stenosis on angiography, including seven patients with 30% to 50% maximum stenosis, four patients with 10% to 20% proximal or ostial narrowing and normal distal coronary arteries, and seven patients with normal angiography. All 11 patients with minimal proximal stenosis or normal coronary arteries had radionuclide perfusion defects involving the inferior or inferoapical regions during exercise as their only sign of ischemia. However, four of the 22 patients (18.2%) with this isolated sign of ischemia had single-vessel stenosis greater than 50% and two (9.1%) had two-vessel disease with stenosis greater than 70%.

A positive stress test was more common in older patients (mean ± standard deviation: 48 ± 10 *v* 41 ± 9 years; $P < .0001$), males (28% *v* 13% for females; $P = .002$), those who had not received doxorubicin (7% doxorubicin *v* 21% no doxorubicin; $P = .02$), and those who had received irradiation earlier (means ± standard deviations: positive, 21 ± 6 *v* negative, 15 ± 7 years earlier; $P = .002$). No other clinical variables including radiation dose were predictive of a true-positive test. The test characteristics are summarized in Table 5.

Events During Follow-Up

During a median 6.5 years (interquartile range, 4.0 to 8.4 years) of follow-up after screening, 23 patients developed symptomatic coronary artery disease, including 10 who sustained an acute myocardial infarction (two fatal). The median time to a cardiac event was 4.6 years (interquartile range, 1.7 to 7.3 years), with six events occurring within 2 years of screening. A total of 69 cardiac events or deaths (n = 41) occurred including new-onset heart failure in 12 patients.

The risk of a cardiac event or death after screening was related to patient age, the latent period, dose of radiation received, the presence of wall motion abnormalities on echocardiography, and ischemia on stress testing (wall motion or perfusion). Patients with events tended to be older (46 ± 10 *v* 41 ± 9 years; $P < .0001$), had received irradiation earlier (19 ± 7 *v* 14 ± 7 years; $P < .0001$), had received higher doses of mediastinal irradiation (BED, 73 ± 6 *v* 70 ± 7 units; $P = .008$), were more likely to have abnormal wall motion (34% *v* 15%; $P = .001$), and more likely to have ischemia on stress imaging (23% *v* 12%; $P = .02$) than those without events. In a proportional hazards model the latency period (hazard ratio [HR], 2.73; 95% CI,

Table 4. Comparison of Screening Stress Tests With Coronary Angiography Results

Test Result	No. of Patients	Angiography		> 50% Stenosis		> 70% Stenosis		Three-Vessel or Left Main Disease	
		No.	%	No.	%	No.	%	No.	%
Echocardiography									
Positive	16	15 of 16	94	13 of 15	87	12 of 15	80	7 of 15	47
Negative	276	25 of 276	9	9 of 25	36	4 of 25	16	1 of 25	4
Nuclear perfusion									
Positive	32	29 of 32	91	13 of 29	45	9 of 29	31	2 of 29	7
Negative	242	9 of 242	4	7 of 9	78	5 of 9	56	4 of 9	44
Electrocardiography									
Positive	22	8 of 22	36	8 of 8	100	8 of 8	100	8 of 8	100
Negative	260	29 of 260	11	13 of 29	45	7 of 29	24	0 of 29	0

Table 5. Predictive Value of Stress Testing for Coronary Disease After Hodgkin's Disease

Predictive Value	CAD Stenosis Threshold	Stress Echocardiography		Nuclear Scintigraphy		Stress ECG	
		No.	%	No.	%	No.	%
Positive	≥ 70%	12 of 15	80	9 of 29	31	8 of 8	100
	≥ 50%	13 of 15	87	13 of 29	45	8 of 8	100
False positive	≥ 50%	2 of 18	11	16 of 18	89	0 of 16	0
Sensitivity	≥ 50%	13 of 22	59	13 of 20	65	8 of 21	38
Specificity	≥ 50%	16 of 18	89	2 of 18	11	16 of 16	100
False negative	≥ 50%	9 of 22	41	7 of 20	35	13 of 21	62

Abbreviation: CAD, coronary artery disease.

1.81 to 4.11 per 10 years), age (HR, 1.34; 95% CI, 1.03 to 1.76 per 10 years), dose of irradiation (HR, 1.04; 95% CI, 1.00 to 1.09 per BED unit), and presence of wall motion abnormalities (HR, 1.32; 95% CI, 1.01 to 1.72) were associated with event-free survival.

In the cohort of 972 Hodgkin's disease patients who received ≥ 35 Gy to the mediastinum and resided in northern California, 53 of 345 deaths were attributed to heart disease (5.5% overall; relative risk, 4.7; 95% CI, 3.4 to 5.9; absolute risk, 33.4 excess death per 10^4 person-years). Table 6 summarizes the risks for death attributed to acute myocardial infarction, confirms increased risks at all intervals after irradiation, and shows a higher risk among males than females. Nine of the 33 deaths from acute myocardial infarction (27%) occurred before 40 years of age; 14 (42%) occurred within 10 years of treatment for Hodgkin's disease.

DISCUSSION

By screening with stress echocardiography and nuclear scintigraphy, we found a 2.7% prevalence of severe, three-vessel, or left main coronary artery disease, and a 7.5% prevalence of coronary stenosis greater than 50% in patients treated with mediastinal irradiation in doses of ≥ 35 Gy for Hodgkin's disease at a mean of 15 years following irradiation. This is an underestimation of the prevalence of coronary disease, given that patients were not required to undergo angiography and were excluded if they had known coronary disease. In previous screening studies, 5.3% (two of 38) and 4% (five of 144) of Hodgkin's disease patients had signs of stress-induced ischemia on perfusion scintigraphy or electrocardiography.[18,20] Myocardial perfusion was considered abnormal on scintigraphy in 14 (61%) of 23 Hodgkin's disease patients studied in Sweden.[39] Among 25 patients studied in France, 21 (84%) had abnormal perfusion scintigraphy, and most patients had myocardial sectors that had significantly lower thallium uptake than corresponding sectors measured in unirradiated individuals considered at low risk for coronary disease.[40] The authors of the latter study considered the patterns of impaired perfusion atypical for major coronary artery obstruction. They attributed exercise-induced defects to disease in small coronary arteries and attributed fixed perfusion defects to myocardial fibrosis. However, none of these studies used routine coronary angiography to evaluate abnormalities identified on screening studies.

The rates for coronary disease that we observed are higher than reported in studies that have screened general populations for coronary disease. Screening identified three-vessel disease in 1.1% of asymptomatic men in the United States military of similar age to our cohort.[41] Sequential screening tests of male government workers in Italy identified 0.5% with ≥ 50% coronary stenosis.[42] Our screened cohort included women and fewer patients with conventional coronary risk factors than the cohorts in those studies. Glanzmann et al[20] found that increased risks for ischemic heart disease were confined to irradiated individuals who had conventional cardiac risk factors. In our study population, conventional risk factors for coronary artery disease, such as older age, tobacco use, diabetes, hypertension, and dyslipidemia, were uncommon and were insensitive indications of coronary risk after mediastinal irradiation.

The severity of coronary disease identified in our patients by screening was similar to that observed among men with definite angina pectoris in the Coronary Artery Surgery Study (CASS) study.[43] More than half of those with identified coronary disease had at least

Table 6. Mortality From Acute Myocardial Infarction Among 972 Patients Treated for Hodgkin's Disease

Patient Group	No. at Risk	Observed/Expected Events	Relative Risk	95% CI	Absolute Risk*
All patients†	972	33 of 4.39	7.5	5.0 to 10.1	22.9
Males	531	28 of 3.43	8.2	5.1 to 11.2	36.4
Females	441	5 of 0.96	5.2	1.7 to 12.1	7.1
Within 10 years of irradiation	972	14 of 1.91	7.3	4.0 to 10.5	15.6
10 through 19 years after irradiation	565	13 of 1.61	8.1	4.3 to 12.4	30.3
> 20 years after irradiation	213	6 of 0.87	6.9	2.5 to 15.1	53.0

*Excess deaths per 10,000 person-years of observation.
†Patients treated at Stanford University Medical Center with ≥ 35 Gy to the mediastinum who resided in Northern California.

one stenosis ≥ 70% or left main stenosis ≥ 50%. The high rates of significant ostial stenosis in our patients (15% left main, 13% right main) parallels the 16% rate of left main ostial stenosis observed in men with definite angina pectoris in the CASS registry. Ostial stenosis was notably common in a small study of irradiated patients but affected 0.13% to 2.6% of patients in published series of consecutive patients undergoing angiography.[10,44] The high rate of proximal coronary artery disease may account for the increased risks of fatal myocardial infarction and sudden cardiac death documented in this and previous reports.

The true prevalence of severe coronary stenosis may be higher than we documented. Four patients with abnormal stress imaging refused coronary angiography. Among the screened cohort, 24% developed symptomatic heart disease, including 8% with documented coronary insufficiency or death. In a prior study using our cohort we found a high rate of diastolic dysfunction on resting echocardiography, suggesting an increased rate of ischemic heart disease, although the relationship with coronary artery disease was not investigated.[25] Additional studies are needed to determine if diastolic function can be used as screening for coronary disease after irradiation.

Screening for coronary disease is useful only if treatment is available that will improve outcome. Few of our patients had conventional, modifiable risk factors for coronary disease. Coronary artery bypass grafting was used to treat eight of 15 patients with coronary disease documented by angiography in our study. Although physicians identified symptoms of ischemia in several patients after abnormal screening tests, most patients were truly asymptomatic, and all patients were judged to be free of cardiac symptoms during clinic evaluations before screening. Although most trials of coronary artery bypass surgery have documented a benefit only in symptomatic patients, surgery yielded a similar survival benefit for asymptomatic or symptomatic patients with left main coronary disease in the CASS study.[33]

Our study compared several screening tests that were recorded during a single stress session. As reported in prior studies of nuclear scintigraphy,[41,45] stress-induced perfusion defects proved a less specific sign of significant coronary disease than other tests: 55% of patients with positive studies had no coronary stenoses exceeding 50% on angiography. Such findings may be due to actual perfusion defects caused by small-vessel obstructive disease, endothelial dysfunction, or vascular spasm, or due to false positive tests, where perfusion is actually normal.

We were unable to delineate the importance of radiation dose and dose-intensity due to the limited variation in total mediastinal radiation dose (70% of the patients received mediastinal radiation doses of 43 to 45 Gy). The use of the BED may not completely control for differences in irradiation practices over time. The lower probability of identifying coronary disease on screening within 10 years of therapy may relate to decreased total radiation dose, volume, and dose-intensity in more recently treated patients.

In summary, we found high prevalence rates for stress-induced radionuclide perfusion defects or wall motion abnormalities on echocardiography that led to identification of severe three-vessel or left main coronary disease and prompted revascularization in asymptomatic patients after mediastinal irradiation for Hodgkin's disease. Conventional risk factors for coronary disease were uncommon and did not predict coronary disease. These findings suggest that screening for coronary artery disease should be considered during follow-up care for asymptomatic patients who have received mediastinal irradiation to doses of 35 Gy or more. Although the diagnostic yield will be greater for patients more than 10 years beyond irradiation, we recommend initiating screening 5 years after treatment, given increased risks for cardiac death and myocardial infarction within 5 to 10 years of initial therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

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ERRATUM

The January 1, 2007 article by Heidenreich et al entitled, "Screening for Coronary Artery Disease After Mediastinal Irradiation for Hodgkin's Disease" (J Clin Oncol 25:43-49, 2007) contained errors.

In the Patients and Methods section, under Statistical Analyses, the description of the initial multivariate models was given as:

"Multivariate models initially included the following **dependent** variables: age, sex, hypertension (yes/no), diabetes (yes/no), low-density lipoprotein and high-density lipoprotein cholesterol, smoking history (yes/no), chemotherapy (yes/no), irradiation dose in BED, and time after irradiation. Variables were removed from the model sequentially, until only those variables that were predictors ($P < .05$) of the **independent** variable remained."

While it should have read:

"Multivariate models initially included the following **independent** variables: age, sex, hypertension (yes/no), diabetes (yes/no), low-density lipoprotein and high-density lipoprotein cholesterol, smoking history (yes/no), chemotherapy (yes/no), irradiation dose in BED, and time after irradiation. Variables were removed from the model sequentially, until only those variables that were predictors ($P < .05$) of the **dependent** variable remained."

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