

Management of Breast Cancer After Hodgkin's Disease

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Purpose: To evaluate the incidence, detection, pathology, management, and prognosis of breast cancer occurring after Hodgkin's disease.

Patients and Methods: Seventy-one cases of breast cancer in 65 survivors of Hodgkin's disease were analyzed.

Results: The median age at diagnosis was 24.6 years for Hodgkin's disease and 42.6 years for breast cancer. The relative risk for invasive breast cancer after Hodgkin's disease was 4.7 (95% confidence interval, 3.4 to 6.0) compared with an age-matched cohort. Cancers were detected by self-examination (63%), mammography (30%), and physician exam (7%). The histologic distribution paralleled that reported in the general population (85% ductal histology) as did other features (27% positive axillary lymph nodes, 63% positive estrogen receptors, and 25% family history). Although 87% of tumors were less than 4 cm, 95% were

managed with mastectomy because of prior radiation. Two women underwent lumpectomy with breast irradiation. One of these patients developed tissue necrosis in the region of overlap with the prior mantle field. The incidence of bilateral breast cancer was 10%. Adjuvant systemic therapy was well tolerated; doxorubicin was used infrequently. Ten-year disease-specific survival was as follows: in-situ disease, 100%; stage I, 88%; stage II, 55%; stage III, 60%; and stage IV, zero.

Conclusion: The risk of breast cancer is increased after Hodgkin's disease. Screening has been successful in detecting early-stage cancers. Pathologic features and prognosis are similar to that reported in the general population. Repeat irradiation of the breast can lead to tissue necrosis, and thus, mastectomy remains the standard of care in most cases.

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BREAST CANCER IS the most frequently diagnosed malignancy among women in the United States, with a lifetime risk of 12.2%.¹ Although much less common, Hodgkin's disease is one of the most successfully treated malignancies, with cure rates that currently exceed 85%. Women who survive Hodgkin's disease have a substantially higher risk of breast cancer than the general population.² The magnitude of this problem has become more evident as women have reached two or three decades of survival after treatment for Hodgkin's disease. The surgical, radiotherapeutic, and systemic treatment of breast cancer is well established when it presents as a primary malignancy. However, there is little information regarding the optimal management of breast cancer that arises in women previously treated for Hodgkin's disease. This report serves to address issues of prevention, screening, pathology, management, and prognosis of breast cancer in this unique population. The risk of developing breast cancer for patients treated with radiotherapy alone and combined-modality therapy for Hodgkin's disease is updated from the Stanford database.

PATIENTS AND METHODS

Sixty-eight women who had been diagnosed with breast cancer and Hodgkin's disease were identified from a retrospective review of the Radiation Oncology and Medical Oncology clinical databases at Stanford University. Two of these women had developed Hodgkin's disease after diagnosis of breast cancer, and another was diagnosed with both malignancies simultaneously. This analysis is limited to 65 women who developed 71 in-situ or invasive breast cancers before 1997 after treatment for Hodgkin's disease. Fifty-six of these women were among a population of 1,064 women treated for Hodgkin's

disease at Stanford between 1960 and 1997. Nine other patients received treatment for Hodgkin's disease elsewhere but presented to Stanford after a diagnosis of breast cancer. Patients reported in earlier series from our institution were included in this analysis.

The median age of the 65 women at diagnosis of Hodgkin's disease was 24.6 years (range, 13.3 to 71.8 years). Thirty-seven patients (57%) were treated for their Hodgkin's disease with radiotherapy alone, one (2%) received chemotherapy alone, and 27 (41%) had combined-modality therapy. The majority of women received radiation to lymph node areas above and below the diaphragm during total lymphoid irradiation (29%) or subtotal lymphoid irradiation in which pelvic, inguinal, and femoral nodal regions were unirradiated (49%). As part of this treatment, a standard mantle field irradiated the neck, supraclavicular, infraclavicular, axillary, and mediastinal areas. Nine patients (14%) had only mantle radiation; four women (6%) received radiation limited to involved regions above the diaphragm. The mean radiation dose to supradiaphragmatic fields was 43.4 Gy (range, 24.0 to 51.0 Gy). Among the 28 women who received chemotherapy, 21 (75%) had nitrogen mustard, vincristine, procarbazine, and prednisone (MOPP); two (7%) received MOPP in combination with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), four (14%) were treated with procarbazine, melphalan, and vinblastine (PAVe), and one (4%)

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Table 1. RR of Breast Cancer According to Length of Time Since Treatment for Hodgkin's Disease

Interval From HD (years)	Person-Years at Risk	No. of Events		RR	RR 95% CI	Absolute Risk*
		Observed	Expected			
0-4	4692	2	2.44	0.8	0.1-3.0	-
5-9	3516	7	2.45	2.9	1.1-5.9	12.9
10-14	2479	9	2.40	3.8	1.7-7.1	26.6
15-19	1418	21	1.89	11.1	6.4-15.8	134.7
20	805	11	1.51	7.3	3.6-13.0	117.8
All patients	12,911	50	10.69	4.7	3.4-6.0	30.4

Abbreviation: HD, Hodgkin's disease.

*Absolute risk = number of excess breast cancers diagnosed per 10,000 person-years of observation.

received ABVD alone.³⁻⁵ One patient had undergone dose-intensive chemotherapy and an autologous bone marrow transplant for recurrent Hodgkin's disease.

Breast tumor size, histologic type and grade, estrogen and progesterone receptors, and axillary node status were obtained from original surgical pathology reports. Tumor location was determined by physician and patient descriptions, as well as pathology and mammogram reports. The relationship of breast cancers to prior radiation fields was judged using radiotherapy field photographs, diagrams, and port films. Follow-up information was obtained at routine appointments or by telephone.

The risk of invasive breast cancer relative to a standard population was calculated for the 1,064 women treated for Hodgkin's disease at Stanford using the subject-year method.⁶ The median length of follow-up since the diagnosis of Hodgkin's disease was 21.2 years for this cohort. Person-years of observation were compiled beginning at the initial diagnosis of Hodgkin's disease to the date of last follow-up, death, or diagnosis of breast cancer. The number of expected infiltrating breast cancers was obtained by multiplying the accumulated person-years by age, race, and sex-matched annualized incidence rates from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database. The relative risk (RR) was defined as the ratio of observed to expected cancers. Statistical tests of significance and 95% confidence intervals (CIs) of risk were calculated using exact Poisson probabilities.⁷ Absolute risk was calculated as the number of observed cases minus the expected number of cases, divided by the person-years of observation, and multiplied by 10,000 to estimate the excess number of cases per 10,000 person-years of observation. Patients with carcinoma-in-situ alone or who did not receive Hodgkin's disease treatment at Stanford were not included in the risk analyses.

The median follow-up after the first breast cancer diagnosis was 3 years (range, 0.4 to 17.3 years) for the 65 women in this analysis. A χ^2 analysis with Yates continuity correction was used to detect statistical differences in frequencies. The Kaplan-Meier technique was used to calculate actuarial disease-specific survival from the time of pathologic confirmation of breast cancer.⁸

RESULTS

Breast cancer was diagnosed at a median age of 42.6 years (range, 23.0 to 79.1 years). Seventy-five percent of women were premenopausal. The median interval between Hodgkin's disease and breast cancer was 17.4 years (range, 1.5 to 32.7 years). The RR of invasive breast cancer for all women treated for Hodgkin's disease at Stanford was 4.7 (95% CI, 3.4 to 6.0). This corresponds to an absolute risk of 30.4 (95% CI, 20.0 to 44.6) excess cases of breast cancer per 10,000 person-years of follow-up. As in previous reports,² the RR for breast cancer increased with increasing duration of follow-up after treatment for Hodgkin's disease (Table 1).

The risk of invasive breast cancer was not significantly increased during the first 15 years after treatment with irradiation alone (Table 2). Risk was significantly increased during the first 15 years after treatment for those women exposed to both mantle irradiation and MOPP or PAVE chemotherapy. In contrast to an earlier analysis from the

Table 2. Risk of Breast Cancer According to Treatment for Hodgkin's Disease

Treatment Group	Person-Years at Risk	No. of Events		RR	RR 95% CI	Absolute Risk*
		Observed	Expected			
Radiotherapy alone	5950	23	5.30	4.3	2.6-6.1	29.8
<15 years after radiotherapy alone	4732	6	3.35	1.8	0.6-3.9	-
15 years after radiotherapy alone	1218	17	1.94	8.8	5.1-10.9	123.6
MOPP or PAVE and radiotherapy	5345	24	3.84	6.2	3.7-8.7	37.7
<15 years after MOPP or PAVE and radiotherapy	4521	10	2.69	3.7	1.8-6.8	16.2
15 years after MOPP or PAVE and radiotherapy	824	14	1.15	12.1	6.6-17.3	155.9

*Absolute risk = number of excess breast cancers diagnosed per 10,000 person-years of observation.

Table 3. Location Within the Breast of Cancers in the Current Series Compared With Series of Hodgkin's Disease Survivors and Controls From Memorial Sloan-Kettering Cancer Center*

Location	Stanford HD Survivors		MSKCC HD Survivors		MSKCC Control Series	
	No.	%	No.	%	No.	%
UO	36	58	26	48	580	60
LO	6	10	5	9	115	12
UI	9	14	13	24	124	13
LI	5	8	8	15	76	8
Central	3	5	2	4	76	8
Diffuse	3	5	0	0	0	0

Abbreviations: UO, upper outer quadrant; LO, lower outer quadrant; UI, upper inner quadrant; LI, lower inner quadrant; HD, Hodgkin's disease; MSKCC, Memorial Sloan-Kettering Cancer Center.

*Memorial Sloan-Kettering Cancer Center Study reported by Yahalom et al.⁹

population of women treated for Hodgkin's disease at Stanford,² this trend of increased risk after combined exposure to radiation and chemotherapy regimens that included alkylating agents now persists for women more than 15 years after therapy. As indicated by the overlapping CIs, none of these trends has yet reached statistical significance. Although the risk within 15 years of irradiation alone was not significantly increased, three cases of breast cancer with short latency developed in women who had no chemotherapy exposure. These included two cases of breast cancer 1.5 and 3.4 years after irradiation in women 40 years of age and one case detected in a 30-year-old woman who was treated for Hodgkin's disease 6.4 years earlier.

The majority of breast cancers in this series (63%) were first noted by the patient, and 10% were identified by a physician on physical examination, when the patient was unaware of any abnormality. Screening mammography was credited for detecting 27% of the cancers, including four cancers presenting in women who were 33 to 38 years of age and eight cancers in women who were between 40 and 49 years of age. Because of the recognition of increased risk for breast cancer in the population of women treated at Stanford, the women were generally advised to undergo screening during follow-up. Nine of 20 diagnosed breast cancers during that interval (45%) were detected by mammography in women who had no abnormalities identifiable on breast examination. Twenty-five percent of patients had a family history of breast cancer in one or more first- or second-degree relatives.

The location of breast cancers could be determined in 62 of the 71 cases. Three women had diffuse disease or large tumors involving multiple quadrants. Among the women for whom the breast cancer location was known, 83% of breast cancers developed within or at the margin of a prior radiotherapy field. The average dose to the breast tissue was 43.4 Gy (range, 24.0 to 51.0 Gy). Three women developed tumors in radiotherapy fields that had received less than 40

Gy. The doses delivered in these cases were 24, 35, and 39 Gy. The majority of cancers (58%) presented in the upper outer quadrants (Table 3). Two women had multifocal disease within the upper outer quadrant. For comparison, Table 3 also includes quadrant distributions from another large series of breast cancer among former patients with Hodgkin's disease and controls from Memorial Sloan-Kettering Cancer Center.^{9,10} Differences between the series were not statistically significant.

Nine breast cancers (13%) were judged to be noninvasive: eight were classified as ductal carcinoma-in-situ (DCIS), and one was lobular carcinoma-in-situ (LCIS). The remaining 62 neoplasms represented invasive carcinoma. The majority were invasive ductal carcinomas (85%), similar to the prevalence of this histology in the general breast cancer population. Among the nine low-grade infiltrating ductal carcinomas were one medullary, one mucinous, and two tubular carcinomas. The distribution of histology and grade is detailed in Table 4. Estrogen receptor testing was performed and available in 30 cases; results were positive in 19 tumors (63%).

Six women (10%) developed bilateral breast cancer. Three women (5%) were diagnosed with synchronous carcinomas when subclinical abnormalities were detected in

Table 4. Distribution of Breast Cancer Histology and Grade

Histology	Patients	
	No.	%
Noninvasive		
Ductal	8	11
Lobular	1	1
Invasive		
Ductal		
Grade 1	9	13
Grade 2	32	45
Grade 3	19	27
Lobular	2	3

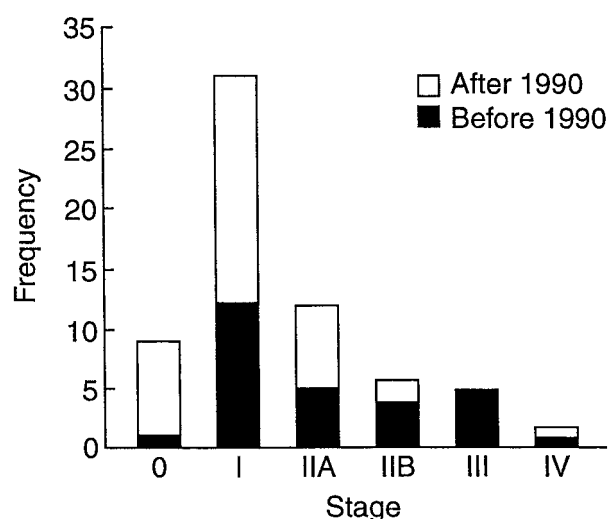


Fig 1. Distribution of breast cancer stages before 1990 and from 1990 to 1997, when increased awareness of breast cancer risk led to increased screening.

the contralateral breast by mammography at ages 38, 43, and 50. Three women (5%) developed a metachronous cancer in the contralateral breast. The second breast cancers were detected by mammography in two women at ages 33 and 43 and by self-examination in another woman at age 51. The time intervals between the breast cancers were 1.7, 3.5, and 11.0 years. Three women with unilateral breast cancer chose to undergo prophylactic contralateral mastectomy. No malignancies or other pathologic abnormalities were detected in these specimens. Fifty-nine women remained at risk for developing a metachronous contralateral breast cancer and have accrued 221.3 person-years of observation after the first breast cancer, for a rate of 13.6 breast cancers per 10,000 person-years of observation. None of the patients with bilateral tumors had a family history of breast cancer in a first- or second-degree relative.

Size measurements were available for 54 of the 62 invasive cancers. Thirty-four tumors (63%) were classified as T1 (≤ 2 cm). Fifteen tumors (28%) measured more than 2 cm but ≤ 5 cm (T2), five cancers (9%) were larger than 5 cm. Pathologic axillary lymph node status was documented in 55 cases, and 15 specimens (27%) were positive. Tumor-node-metastasis staging was determined for 56 cases of invasive cancers as follows: 31 cases (55%) were stage I, 18 (32%) were stage II, five (9%) were stage III, and two (4%) were stage IV. The stage distribution for all cancers is illustrated in Fig 1 and is divided by cancers diagnosed before and after 1990. Before 1990, 13 of 28 women were diagnosed with stage 0 to I cancers, whereas from 1990 onward, 27 of 37 had stage 0 to I disease at diagnosis. This difference was statistically significant ($P = .05$).

DCIS was managed surgically. Four women underwent simple mastectomy; two had wide excision, one had a modified radical mastectomy, and one had a subcutaneous mastectomy. The latter was performed at an outside institution in 1979. This patient developed brain metastases attributed to breast carcinoma 10 years later without evidence of a local recurrence or new primary and died the following year. No other woman with carcinoma-in-situ has developed invasive breast cancer or metastasis. The women who underwent wide excisions had small (< 1 cm), low-grade DCIS and did not receive adjuvant radiotherapy. Their breast cancers have not recurred with follow-up intervals of 10 and 42 months. One patient with DCIS and one patient with LCIS received adjuvant hormonal therapy on a prophylactic treatment protocol. The patient with LCIS had only a biopsy and is receiving careful screening for an invasive tumor.

Invasive cancers were managed by mastectomy in 59 cases (95%). Fifty-five were modified radical, three were simple (no lymph node dissection), and one was a radical mastectomy performed 18 years before this analysis. Two women underwent lumpectomy with axillary node dissection plus radiotherapy. One patient refused additional treatment after excisional biopsy. Unusually poor wound healing was reported after two mastectomies (3%), and one woman suffered a pneumothorax postoperatively. There have been no reports of excessive arm edema after surgery despite prior axillary and supraclavicular irradiation of Hodgkin's disease.

The two patients treated with breast conserving surgery and radiation received that therapy at outside institutions. The first patient developed a stage T1 primary cancer in the upper outer quadrant of the breast, which was not irradiated during Hodgkin's disease radiotherapy. After breast surgery, she was treated with tangentially oriented radiation fields matched to her prior mediastinal field to prevent overlap. She received 46 Gy to the breast and a 20-Gy interstitial boost to the tumor bed. She has not experienced a recurrence or complication after 14 years. A second patient developed a stage T1c, high-grade invasive ductal carcinoma in the upper inner quadrant of the breast 12.7 years after she had been treated with 44 Gy to a mantle field and six cycles of MOPP chemotherapy for Hodgkin's disease. She was treated with tangential breast fields to 45.6 Gy and a boost of 15 Gy to the upper inner quadrant. The breast irradiation fields overlapped the prior mantle field in some regions. This patient returned to Stanford 6 years after the second course of radiation with severe soft tissue necrosis in the lateral breast and chest wall.

Forty-eight percent of women with invasive cancer received adjuvant chemotherapy. Doxorubicin-containing

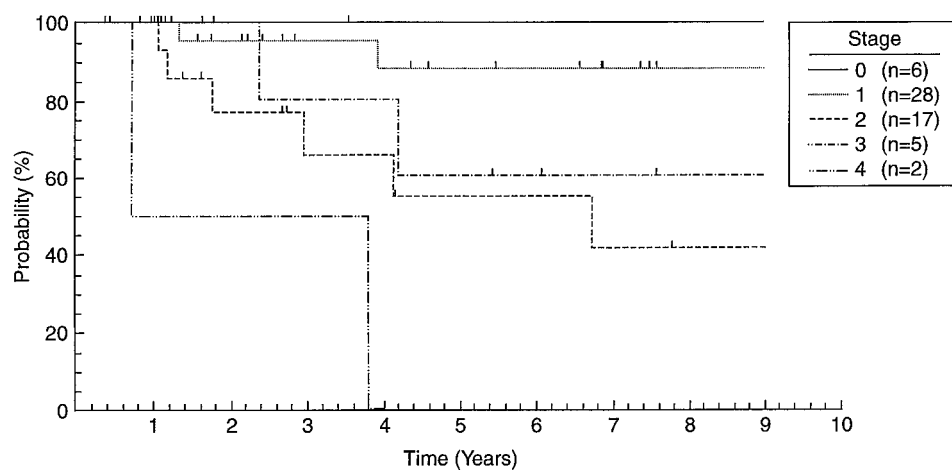


Fig 2. Disease-specific survival for breast cancer, according to stage, in women previously treated for Hodgkin's disease.

regimens were used for two patients who had not received prior chemotherapy for Hodgkin's disease. In one case, doxorubicin was chosen for preoperative treatment in locally advanced breast cancer. Partly because of concerns about prior cardiotoxic chemotherapy and/or radiation, anthracyclines were not used for the remaining 46 women. However, doxorubicin was routinely used for metastatic or recurrent disease. Although no cardiac complications have been reported, follow-up was short in this group of patients, who were expected to have a poor prognosis. Seventeen women with invasive cancer received hormonal therapy. There have been no unusual complications observed with this treatment.

Sixteen women have developed breast cancer metastases, and 15 have died as a result of this malignancy. Five patients developed a chest wall recurrence of breast cancer after mastectomy. Four of these were treated with chest wall radiotherapy and two women received concomitant hyperthermia. These patients had all received mantle radiotherapy for Hodgkin's disease. There were no apparent complications from radiation overlap, but all women died within 2 years of this treatment.

Actuarial disease-specific survival according to stage is illustrated in Fig 2. Patients with DCIS have an actuarial 5-year disease-specific survival of 100%, although there was one late death at 11 years. The disease-specific survival rate at 5 years, according to stage, is as follows: 88% for stage I, 55% for stage II, 60% for stage III, and 0% for stage IV. Two women died of third malignancies (lung and bladder cancer at 5.4 and 7.5 years after breast carcinoma, respectively). Three women died because of myocardial infarction at ages 45, 57, and 60 years. The other unrelated death was from Parkinson's disease. None of these patients had evidence of breast cancer at the time of death. Fifteen

(1.4%) of the 1,064 female survivors of Hodgkin's disease at Stanford have died of breast cancer.

DISCUSSION

The link between breast cancer and treatment for Hodgkin's disease has been documented in many retrospective studies.^{2,11-23} A significantly increased risk seems to be limited to women who had radiation exposure before 30 years of age.^{2,15} The earliest apparent case of breast cancer in this series that seemed likely to have been associated with therapy developed 6.4 years after irradiation for Hodgkin's disease, at 23 years of age. Although three cases of breast cancer were diagnosed at shorter intervals of 1.5 to 3.9 years, they developed at ages (42, 44, and 71 years) that are more typical for breast cancer and may have been coincident with Hodgkin's disease. It is not known whether chemotherapy exposure significantly increases the risk of breast cancer associated with irradiation. However, the excess risk of breast cancer within 15 years of therapy in this population seems to have been confined to the cohort who received combined-modality treatment with regimens containing alkylating agents.

The risk of breast cancer first becomes significantly elevated in years 5 through 9 of follow-up. Thus, we recommend that screening begin 5 years after radiotherapy or at age 40, whichever occurs first. Patients should be instructed how to perform breast self-examination and be encouraged to do so at follow-up evaluations. Women should also have annual clinical breast examination and mammography beginning 5 years after radiation exposure.

The median age at diagnosis of breast cancer was 43 years in this series, which is the same as that reported for 37 patients with breast cancer after Hodgkin's disease at the Memorial Sloan-Kettering Cancer Center.⁹ This is signifi-

cantly lower than the median age of 57 years reported for patients with breast cancer in the general population.²⁴ Young women tend to have dense breast tissue, which is known to make mammograms more difficult to interpret.²⁵ Despite this limitation, young women have had positive screening mammograms in our series and others.²⁶ Screening has been effective in detecting breast cancers at earlier stages (Fig 1), including preinvasive lesions, because more intensive screening for breast cancer has been used in survivors of Hodgkin's disease since 1990.

The fraction of patients with a family history of breast carcinoma (25%) was similar to the rate reported for all breast cancer in the United States.²⁷ It is not known if genetic abnormalities play a role in the higher risk of breast cancer observed after Hodgkin's disease. Candidate genes include ataxia telangiectasia mutation heterozygosity, which is known to increase radiation sensitivity and may increase the risk of radiation-induced breast cancer.²⁸ Other tests for mutations in genes such as *p53*, *BRCA1*, and *BRCA2*, may be helpful in determining individual susceptibility in those women who have a strong family history in addition to radiation exposure.²⁹⁻³¹

Six women (9%) have developed bilateral breast cancer. Three women (5%) had synchronous tumors. This is slightly higher than the 3% rate of simultaneous bilateral disease reported in a population of spontaneous breast cancer patients enrolled onto a prospective clinical trial.³² Although the rate of bilateral cancer may be increased relative to the general population, it is lower than the 29% rate reported by Bhatia et al¹³ and 22% rate reported by Yahalom et al,⁹ with a similar average period of follow-up of 3 years.^{13,9} The contralateral breast cancers identified in our cohort were diagnosed at early stages (Tis-T1bN0M0).

The incidence of a contralateral, metachronous breast cancer is 1.36% per year based on our current data. Although this estimate is derived from limited follow-up, the magnitude of risk does not seem to warrant surgical prophylaxis. Furthermore, second tumors seem to be detectable quite early with vigilant screening. The decision to undergo prophylactic mastectomy is highly personal and may be influenced by a patient's family history, genetic testing results, and psychologic profile. Tamoxifen plays a role in the prevention of second breast cancers in high-risk women and may be appropriate for some patients with Hodgkin's disease.³³

Most women with invasive breast cancer in this series underwent a modified radical mastectomy. Although an axillary dissection usually yielded only five to 10 lymph nodes after therapeutic radiation, the proportion of patients with involved nodes (27%) was similar to the T-stage adjusted rate in the general breast cancer population.³⁴ As in

spontaneously arising in-situ breast cancers, excision without irradiation may be appropriate in selected patients. The role of radiotherapy for DCIS with favorable features needs to be defined by randomized trials.

Reconstruction after mastectomy is an important option for women and should be discussed before definitive surgery. A transverse rectus abdominis myocutaneous flap may be performed in women who have received radiotherapy for Hodgkin's disease. However, prior radiation may affect the integrity of small- and medium-size blood vessels. If flap reconstruction is planned, preoperative ultrasound of the internal mammary artery is recommended to confirm patency. This test was performed for seven women in this series; one woman was found to have significant stenosis that precluded flap reconstruction.³⁵

Prior radiotherapy has long been considered an absolute contraindication to breast conserving treatment with radiation at Stanford and most other cancer centers. Conversely, Karasek et al³⁶ recently published a series of six former lymphoma patients treated with lumpectomy and repeat irradiation of the breast. The breasts of these women were treated with 50 to 60 Gy after prior doses of 30 to 44 Gy. No serious adverse effects were reported, with median follow-up of 60 months (range, 15 to 118 months).

Two women treated for Hodgkin's disease at Stanford had breast-conserving therapy, including radiotherapy at other hospitals. In one woman, breast cancer developed in an unirradiated area, and tangential fields were matched to a prior mediastinal field without apparent adverse consequences. However, this technique may not have irradiated the entire breast. The other woman developed breast cancer within the prior mantle field, which had been treated to 44 Gy 12.7 years earlier. She received standard tangential fields that included the entire breast. Six years later, she presented with severe soft tissue necrosis in the lateral breast and chest wall, where the estimated cumulative Gy dose was 89.6. This complication reinforces the theoretical concern about reirradiation to a high cumulative dose. Given these discordant results and the small number of women treated with breast-conserving therapy, we continue to recommend mastectomy as the standard treatment for patients previously irradiated for Hodgkin's disease.

Adjuvant radiation therapy to the chest wall after mastectomy is often recommended for women at high risk of local recurrence.^{37,38} The benefits of adjuvant chest wall radiotherapy must be weighed carefully with the risks of radiation injury in previously irradiated patients with high-risk breast cancer. The decision to use this treatment and the radiation techniques should be individualized. No women in this series received adjuvant chest wall treatment, but four had chest wall radiation at the time of recurrence. No

complications were noted during the short time before the patients died.

Nearly half of the women (48%) in this series received adjuvant chemotherapy. The most commonly used regimen was cyclophosphamide, methotrexate, and fluorouracil. Patients tolerated this treatment without unexpected side effects. Although only two women were treated with adjuvant regimens containing doxorubicin, many received this agent for metastatic or recurrent disease. All such women had been treated with mediastinal radiotherapy, but none had prior exposure to anthracyclines. No cardiac sequelae were reported, but follow-up was limited by poor survival. Hormonal therapy was also frequently prescribed without any unusual side effects.

Disease-specific survival at 5 years was dependent on breast cancer stage (Fig 2). Given the small numbers of women with stages II to IV disease, this stage-specific

survival data is fairly similar to that reported in large breast cancer series.³⁹ A small fraction (1.4%) of Hodgkin's disease survivors at Stanford have died of breast cancer. These women are also at increased risk for other malignancies and serious medical problems, such as cardiovascular disease.⁴⁰

It is important to inform patients of the risk of breast cancer when obtaining informed consent for treatments that include irradiation of breast tissue at young age and to instruct them on the need for subsequent screening. We are hopeful that the risk of breast cancer will be substantially reduced for women receiving modern combined-modality therapy with reduced field sizes and doses of radiation.

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REFERENCES

- Hankey B, Brinton L, Kessler L, et al: SEER Cancer Statistics Review: 1973-1990. Bethesda, MD, NIH Publication 93-2789, 1993
- Hancock SL, Tucker MA, Hoppe RT: Breast cancer after treatment of Hodgkin's disease. *J Natl Cancer Inst* 85:25-31, 1993
- DeVita VT, Canellos GP, Moxley JH: A decade of combination chemotherapy for advanced Hodgkin's disease. *Cancer* 30:1495-1504, 1972
- Horning SJ, Ang PT, Hoppe RT, et al: The Stanford experience with combined procarbazine, Alkeran, and vinblastine (PAVe) and radiotherapy for locally extensive and advanced stage Hodgkin's disease. *Ann Oncol* 3:747-754, 1992
- Bonnadonna G: Chemotherapy strategies to improve the control of Hodgkin's disease. *Cancer Res* 42:4309-4320, 1982
- Armitage P, Berry G: *Statistical Methods in Medical Research* (ed 3). Oxford, England, Blackwell Scientific Publications, 1994, pp 498-491
- Breslow NE, Day NE: *Statistical Methods in Cancer Research* (vol 2): The Design and Analysis of Cohort Studies. Oxford University Press, London, pp 65-70, 131, 1987
- Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. *Am Stat Assoc* 53:457-481, 1958
- Yahalom J, Petrek JA, Biddinger PW, et al: Breast cancer in patients irradiated for Hodgkin's disease: A clinical and pathological analysis of 45 events in 37 patients. *Int J Radiat Oncol Biol Phys* 10:1674-1681, 1992
- Rosen PP, Lesser ML, Senie RT, et al: Epidemiology of breast cancer IV: Age and histologic tumor type. *J Surg Oncol* 19:44-47, 1982
- Wolden SL, Lamborn KR, Cleary SF, et al: Second cancers following pediatric Hodgkin's disease. *J Clin Oncol* 16:536-544, 1998
- Tinger A, Wasserman TH, Klein EE, et al: The incidence of breast cancer following mantle field radiation therapy as a function of dose and technique. *Int J Radiat Oncol Biol Phys* 37:865-870, 1997
- Bhatia S, Robison LL, Oberlin O, et al: Breast cancer and other second neoplasms after childhood Hodgkin's disease. *N Engl J Med* 334:745-751, 1996
- Sankila R, Garwicz S, Olsen JH, et al: Risk of subsequent malignant neoplasms among 1641 Hodgkin's disease patients diagnosed in childhood and adolescence: A population-based cohort study in five Nordic countries. *J Clin Oncol* 14:1442-1446, 1996
- van Leeuwen FE, Klokman WJ, Hagenbeek A, et al: Second cancer risk following Hodgkin's disease: A 20-year follow-up study. *J Clin Oncol* 12:312-315, 1994
- Prior P, Pope DJ: Hodgkin's disease: Subsequent primary cancers in relation to treatment. *Br J Cancer* 58:512-517, 1988
- O'Brien PC, Baton MB, Fisher R: Breast cancer following treatment for Hodgkin's disease: The need for screening in a young population. *Australasian Radiol* 39:271-276, 1995
- Janjan NA, Wilson JF, Gillin M, et al: Mammary carcinoma developing after radiotherapy and chemotherapy for Hodgkin's disease. *Cancer* 61:252-254, 1988
- Boivin JF, Hutchison GB, Zauberg AG, et al: Incidence of second cancers in patients treated for Hodgkin's disease. *J Natl Cancer Inst* 87:732-741, 1995
- Jenkin D, Greenberg M, Fitzgerald A: Second malignant tumors in childhood Hodgkin's disease. *Med Pediatr Oncol* 26:373-379, 1996
- Abrahamsen JF, Andersen A, Hannisdal E, et al: Second malignancies after treatment of Hodgkin's disease: The influence of treatment, follow-up time, and age. *J Clin Oncol* 11:255-261, 1993
- Salloum E, Doria R, Schubert W, et al: Second solid tumors in patients with Hodgkin's disease cured after radiation or chemotherapy plus adjuvant low-dose radiation. *J Clin Oncol* 14:2435-2443, 1996
- Tucker MA: Solid second cancers following Hodgkin's disease. *Hematol Oncol Clin North Am* 7:389-400, 1993
- Lippman ME: Epidemiology of breast cancer, in Lippman ME, Lichter AS, Danforth DN (eds): *Diagnosis and Management of Breast Cancer*. Philadelphia, PA, Saunders, 1988, pp 1-9
- Jeffries DO, Adler DD: Mammographic detection of breast cancer in women under the age of 35. *Invest Radiol* 25:67-71, 1990
- Dershaw DD, Yahalom J, Petrek JA: Breast carcinoma in women previously treated for Hodgkin's disease: Mammographic evaluation. *Radiology* 184:421-423, 1992
- Madigan M, Ziegler R, Benichou C, et al: Proportion of breast cancer cases in the United States explained by well established risk factors. *J Natl Cancer Inst* 87:1681-1685, 1995

28. Swift M, Reitnauer P, Morrell D, et al: Breast and other cancers in families with ataxia-telangiectasia. *N Engl J Med* 316:1289-1294, 1987
29. Ford D, Easton D, Bishop T, et al: Risks of cancer in BRCA1 mutation carriers. *Lancet* 343:692-695, 1994
30. Wooster R, Neuhausen SL, Mangion J, et al: Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. *Science* 265:2088-2090, 1994
31. Malkin D, Li F, Strong L, et al: Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. *Science* 250:1233-1238, 1990
32. Chaudary MA, Millis RR, Hoskins EO, et al: Bilateral primary breast cancer: A prospective study of disease incidence. *Br J Surg* 71:711-714, 1984
33. Nayfield SG, Karp JE, Ford LG, et al: Potential role of Tamoxifen in prevention of breast cancer. *J Natl Cancer Inst* 83:1450-1459, 1991
34. Carter CL, Allen C, Henson DE: Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. *Cancer* 63:181-187, 1989
35. Greenberg L, et al: Post-mastectomy breast reconstruction in women previously irradiated for Hodgkin's disease. *Proc 67th Ann Mtg Am Soc Plast Reconstr Surg* 1998, p 141
36. Karasek K, Deutsch M: Lumpectomy and breast irradiation for breast cancer after radiotherapy for lymphoma. *Am J Clin Oncol* 19:451-454, 1996
37. Overgaard M, Hansen PS, Overgaard J, et al: Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. *N Engl J Med* 337:949-955, 1997
38. Ragaz J, Jackson SM, Le N, et al: Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med* 337:956-962, 1997
39. Fleming ID, Cooper JS, Henson, et al (eds.): *AJCC Cancer Staging Manual* (ed 5). Philadelphia, PA, Lippincott-Raven, 1997
40. Hancock SL, Hoppe RT: Long-term complications of treatment and causes of mortality after Hodgkin's disease. *Semin Radiation Oncol* 6:225-242, 1996