Risk Factors for Locoregional Recurrence Among Breast Cancer Patients: Results From International Breast Cancer Study Group Trials I Through VII

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Purpose: **To explore prognostic factors for locoregional failures (LRF) among women treated for invasive breast cancer within clinical trials of adjuvant therapies.**

Patients and Methods: **The study population consisted of 5,352 women who were treated with a modified radical mastectomy and enrolled in one of seven International Breast Cancer Study Group randomized trials. A total of 1,275 women with node-negative disease received either no adjuvant therapy or a single cycle of perioperative chemotherapy, and 4,077 women with node-positive disease received adjuvant chemotherapy of at least 3 months' duration and/or tamoxifen. Median follow-up is 12 to 15.5 years.**

Results: **In women with node-negative disease, factors associated with increased risk of LRF were vascular invasion (VI) and tumor size greater than 2 cm for premenopausal and VI for postmenopausal patients. Of the 1,275 patients, 345 (27%) met criteria for the highest risk groups, and the 10-year cumulative incidences of LRF with or without distant metastases were 16% for premenopausal and 19% for postmenopausal women. For the node-positive cohort, number of nodes and tumor grade were factors for both menopausal groups, with additional prediction provided by VI for premenopausal and tumor size for postmenopausal patients. Of the 4,077 patients, 815 (20%) met criteria for the highest risk groups, and 10-year cumulative incidences were 35% for premenopausal and 34% for postmenopausal women.**

Conclusion: **LRFs are a significant problem after mastectomy alone even for some patients with node-negative breast cancer, as well as after mastectomy and adjuvant treatment for some subgroups of patients with node-positive disease. In addition to number of positive lymph nodes, predictors of LRF include tumor-related factors, such as vascular invasion, higher grade, and larger size.**

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BEFORE THE ERA of adjuvant systemic therapies, extensive local and regional treatment, often including radiotherapy, was used frequently in the treatment of breast cancer. The addition of radiotherapy to surgery reduced the number of local and regional recurrences. Overviews of all radiotherapy trials indicated reduced breast cancer mortality but failed to show a significant overall survival benefit.[1]

Adjuvant systemic treatment of breast cancer improves the relapse-free survival rate by reduction of local, regional, and distant relapses and moderately improves survival.[2-4] Two randomized clinical trials from Denmark and Canada on radiotherapy together with adjuvant chemotherapy in mainly node-positive premenopausal breast cancer patients[5,6] and one study from Denmark on radiotherapy with tamoxifen in postmenopausal patients[7] found improved survival in the radiotherapy arms. There has been concern that the quality of the axillary surgery in the Danish study, in which a median of only seven removed lymph nodes were investigated, as well as less optimal adjuvant chemotherapy[8,9] may have contributed to a high risk of cancer remaining in the locoregional area.

Recent consensus statements have concluded that locoregional radiotherapy might be considered to improve the relapse-free and possibly overall survival for some patients who are at high risk for locoregional relapse of the disease despite adjuvant systemic treatment.[10-14] Because radiotherapy is resource consuming and may be followed by severe late effects, it should be reserved for patients who are at high risk. Thus there is a need to explore the incidence of locoregional relapses after controlled surgery and in connection with systemic treatment. In the International Breast Cancer Study Group (IBCSG, formerly the Ludwig group), a minimum number of removed lymph nodes were required before patients could be included in the trials. A previous publication from the IBCSG showed that more effective systemic treatments reduced the risk of local and regional recurrences compared with the less effective treatments for patients with node-positive disease.[15]

The aim of the present study was to expand on these results by defining risk groups for locoregional recurrence (with or without simultaneous distant failure) in patients who were treated with mastectomy and enrolled in one of seven IBCSG trials.

PATIENTS AND METHODS

Designs of the Studies

The analysis was based on information collected on patients selected from IBCSG trials I through VII and fulfilling the criteria described below.

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Detailed definitions for menopausal status, patient characteristics, and eligibility have been described elsewhere.[16-24] With the exception of trial V, in which patients were included before the pathologic work-up was completed, patients were only included if the tumors were stage pathologic (p) T1, pT2, or pT3 (tumor-node-metastasis staging system), margins of resection were free of tumor cells, and there was no involvement of skin or fascia. At least eight lymph nodes from the axilla had to be examined. The characteristics of the patients of the individual trials follow.

In trials I and II, pre- and perimenopausal women with axillary lymph node–positive disease were randomly assigned between July 1978 and August 1981. All patients in trial I were treated with 12 28-day courses of classic cyclophosphamide, methotrexate, and fluorouracil (CMF; cyclophosphamide 100 mg/m^2 orally days 1 to 14, methotrexate 40 mg/m^2 administered intravenously [IV] days 1 and 8, and fluorouracil 600 mg/m^2 IV days 1 and 8, repeated every 28 days), and all patients in trial II were treated with 12 28-day courses of CMF plus low-dose prednisone (7.5 mg/m^2 orally [PO] daily) for 1 year (CMFp). The addition of low-dose prednisone to CMF was studied in trial I (patients with one to three lymph node metastases), and the addition of oophorectomy to CMFp was studied in trial II (patients with $\geq$ four lymph node metastases). All patients received mastectomy and no radiotherapy.

In trials III and IV, postmenopausal patients with axillary lymph node–positive disease were randomly assigned between July 1978 and August 1981. Tamoxifen 20 mg PO daily plus low-dose prednisone for 1 year was compared with observation alone (trial IV, patients older than 65 years), or a regimen of 12 28-day courses of CMF plus low-dose prednisone and tamoxifen for 1 year was compared with tamoxifen plus low-dose prednisone for 1 year and with observation alone (trial III, patients 65 years of age or younger). All patients received mastectomy and no radiotherapy.

Trial V included pre- or postmenopausal women who between November 1981 and December 1985 were randomly assigned at the time of surgery to one course of perioperative (commencing within 36 hours of surgery) IV CMF (PeCMF; cyclophosphamide 400 mg/m^2 IV days 1 and 8, methotrexate 40 mg/m^2 IV days 1 and 8, fluorouracil 600 mg/m^2 IV days 1 and 8, and leucovorin 15 mg IV 24 hours after day 1 and 15 mg PO 24 hours after day 8) or no such treatment. After pathologic work-up, patients with no involvement of axillary lymph nodes received no further treatment. Patients with axillary lymph node involvement received either six 28-day courses of classic CMFp or no further chemotherapy. Tamoxifen for 6 months was given with the CMFp for postmenopausal women. All patients received mastectomy and no radiotherapy.

Trial VI was open for pre- and perimenopausal patients with lymph node–positive breast cancer between July 1986 and April 1993. The patients received three or six courses of classic CMF initially and an additional zero or three courses of the same chemotherapy 3, 6, and 9 months after the initial courses (late reintroduction).

Trial VII included postmenopausal patients between July 1986 and April 1993. All patients received tamoxifen for 5 years. They were randomly assigned to receive either three courses of classic CMF initially or no initial treatment. Irrespective of the first treatment, patients were also randomly assigned to receive no further treatment or three courses of classical CMF at months 9, 12, and 15 (delayed chemotherapy). No radiotherapy was given after mastectomy in trials VI and VII.

Patient Selection

The patients were selected from these trials and fulfilled the following criteria: (1) The initial surgery included a total mastectomy (patients treated with breast-conserving surgery in trials VI [433 patients] and VII [285 patients] were excluded); (2) all 1,275 patients with node-negative disease (all from trial V) were included in the analyses (one third of these patients received no adjuvant therapy and two thirds received a single cycle of PeCMF); (3) in pre- and perimenopausal patients with node-positive disease, at least three courses of CMF were to be given (240 patients with node-positive disease in trial V who received only one course of PeCMF were excluded); (4) in postmenopausal patients with node-positive disease, either at least three courses of CMF or tamoxifen for 1 to 5 years was given (patients given only one course of PeCMF in trial V [173 patients] or randomized to no adjuvant treatment in trials III [156 patients] or IV [153 patients] were excluded). Thus, 722 patients with node-positive disease who received less effective adjuvant therapy[15] and 718 patients who received breast-conserving surgery were excluded from these analyses. In these studies, 91% of all patients (for both node-negative and node-positive cohorts) had eight or more nodes examined, with 46% (44% for node-negative and 47% for node-positive) having 15 or more nodes examined.

For trials I through V, a central pathology review process was conducted. The central review included the histologic evaluation of biopsy and mastectomy specimens for invasion of any vessel space, lymphatic or blood vessel, around the primary tumor.[25,26] Vessel invasion (VI) was defined as the presence of tumor cell emboli within a vessel space, which were identified by associated fibrin clot and/or an endothelial cell lining. The study protocol required that at least two sections of primary tumor be taken at right angles to one another to include the interface of the growing tumor border and the adjacent breast tissue. Generally, approximately 6 cm^2 of breast tissue immediately adjacent to the primary tumor but within 1 cm of the tumor border was available for the assessment of peritumoral vessel invasion. For trials VI and VII, no central pathology review process was in place, and the information about vessel invasion was provided by the local pathology work-up from the participating centers.

Statistical Analysis

We used information from 5,352 patients, with a median follow-up (FU) of 14.5 years. On the basis of the eligibility criteria of the clinical trials included, analyses were conducted separately on the following four patient cohorts: premenopausal, node-negative cohort from trial V (692 patients; median FU, 15.3 years); postmenopausal, node-negative cohort from trial V (583 patients; median FU, 15.5 years); premenopausal, node-positive cohort from trials I, II, V, and VI (2,335 patients; median FU, 13.3 years); and postmenopausal, node-positive cohort from trials III, IV, V, and VII (1,742 patients; median FU, 12.0 years).

The following variables and categories were defined for the analysis: nodal status (zero, one to three, or four or more involved nodes), tumor size ($\leq$ 2 cm or $>$ 2 cm), estrogen receptor status (negative [$<$ 10 fmol/mg of cytosol protein] or positive), age ($<$ 60 or $\geq$ 60 years), histologic grade (1, 2, or 3), and vessel invasion (yes or no). Some of these variables were missing for some of the patients. In particular, estrogen receptor status, histologic grade, tumor size, and vessel invasion were not always known, because these variables were not required for the inclusion of patients into the trials. We included an additional category (unknown) for those variables to capture this possibility.

Because we focused on patient- and disease-related features, we did not include type of adjuvant systemic therapy as a variable to define risk factors. All women with node-positive disease received at least 3 months of chemotherapy and/or at least 1 year of tamoxifen per randomized assignment; 92% received at least 6 months of chemotherapy and/or 5 years of tamoxifen. For women with node-negative disease, one third received no adjuvant therapy and two thirds received a single cycle of PeCMF according to randomized assignment in trial V. Secondary analyses of locoregional recurrence according to treatment were conducted for the node-negative cohort.

Locoregional recurrence was defined as a first relapse on the chest wall, the ipsilateral axilla, ipsilateral supraclavicular or infraclavicular fossa, or the ipsilateral internal mammary region. Categories of sites of failure of interest (as site of first event) were as follows: isolated locoregional (locoregional failure [LRF] without simultaneous distant relapse); locoregional with or without simultaneous distant (LRF $\pm$ distant failure [DF]); distant alone (DF). When analyzing each of the sites of failure, we treated the other possible first events as competing events, thus also considering LRF + DF events to obtain mutually exclusive events.

LRF $\pm$ DF events were used to define risk groups separately for each of the four cohorts of patients, as follows. A regression model for the cumulative incidence function[27] was used. To perform model selection, one variable at a time was first introduced in the model. If the inclusion of that variable added one parameter to the model, then the need for that variable in the model was judged on the basis of the *P* value of the parameter. When more than one indicator was needed to code the variable, then a Wald-type test was used to judge the significance of that covariate. After the variables that should appear in the model were individually selected, these were all introduced together. Likelihood ratio tests[28] were then used to determine which of the variables should be kept in the model and which could be dropped. Variables with a *P* value greater than .05 were dropped. Reintro-

duction of previously discarded variables was tested at each step at the .10 level. Model selection was performed separately for each of the four groups.

A risk index (RI) was then constructed on the basis of each selected regression model. The RI is defined as **b**'**Z**, where **b** is the estimated vector of the regression coefficients, and **Z** is the vector of covariates in the model. The RI was computed and its observed distribution was used to find three cutoff points that would divide the patients into four groups of approximately the same size (25% of the total), with the groups having increasing risk. We labeled the four groups as having low, medium, high, and very high risk. These labels reflect the relative risk of failure within a given patient cohort and not the absolute level of risk. When the number of significant factors did not allow the definition of four risk groups, we proceeded with a smaller number of groups. To take advantage of the information contained in the data arising from patients who had one or more covariates missing, all combinations of covariate values (including missing values) were used to construct the risk groups.

The combinations of the values of the covariates to which each risk category corresponded were then identified so that a map from risk factor combinations to risk groups was constructed. Finally, we estimated the cumulative incidence function (CIF)[29,30] at 10 years for each of the sites of failures for the four risk groups and calculated estimates of 10-year overall survival for each risk group. We also report the estimated CIF curves for LRF ± DF events for the risk groups identified within each of the four patient populations.

RESULTS

Table 1 lists the patient population characteristics overall and within each of the four cohorts of patients selected for the analysis. The percentage of patients having a particular covariate missing ranged from 2% to 25%. There were two patients (in trial V) who were 60 years of age and premenopausal. The exact site of failure was unknown for a total of 21 deceased patients. These patients have been assigned to the "other" category for site of failure. Table 2 lists the observed number of patients for each of the site of failure groups considered for the analysis. In total, 1,138 patients experienced LRF (with or without DF) as a first event. The site of LRF was local for 53%, supra-/infraclavicular for 26%, axilla for 13%, internal mammary for 1%, and multiple LRF regions for 7% of patients.

Premenopausal Patients With Node-Negative Disease

The regression model showed that tumor size ($P = .027$) and VI ($P = .023$) were prognostic factors for LRF ± DF. Either the presence of VI or a large tumor contributed similarly to the increase in risk of failure, and a medium-risk/high-risk group

Table 1. Patient Characteristics

	All Patients		Premenopausal Node-Negative		Postmenopausal Node-Negative		Premenopausal Node-Positive		Postmenopausal Node-Positive	
	No.	%	No.	%	No.	%	No.	%	No.	%
Total	5,352	100	692	100	583	100	2,335	100	1,742	100
Trial										
I	491	9					491	21		
II	327	6					327	14		
III	307	6							307	18
IV	167	3							167	10
V	2,091	39	692	100	583	100	475	20	341	20
VI	1,042	20					1,042	45		
VII	927	17							927	53
Age, years										
< 60	4,043	76	691	100	297	51	2,334	100	721	41
≥ 60	1,309	25	1	0	286	49	1	0	1,021	59
Menopausal status										
Pre	3,027	57	692	100			2,335	100		
Post	2,325	43			583	100			1,742	100
Nodes										
None	1,275	24	692	100	583	100				
1-3	2,404	45					1,395	60	1,009	58
4+	1,673	31					940	40	733	42
Tumor size										
≤ 2 cm	2,179	41	365	53	321	55	844	36	649	37
> 2 cm	2,973	55	276	40	230	39	1,412	61	1,055	61
Unknown	200	4	51	7	32	6	79	3	38	2
Tumor grade										
1	726	14	84	12	116	20	299	13	227	13
2	2,017	38	287	42	232	40	845	36	653	38
3	1,519	28	242	35	190	33	662	28	425	24
Unknown	1,090	20	79	11	45	8	529	23	437	25
Estrogen receptor status										
0-9	1,525	29	249	36	160	27	717	31	399	23
10+	2,898	54	304	44	336	58	1,196	51	1,062	61
Unknown	929	17	139	20	87	15	422	18	281	16
Vessel invasion										
No	2,254	42	368	53	322	55	870	37	694	40
Yes	2,433	46	278	40	225	39	1,142	49	788	45
Unknown	665	12	46	7	36	6	323	14	260	15

Table 2. Summary of Failures Observed

Trial	Median Follow-Up (years)	No. of Patients	LRF Only (no. of failures)	LRF ± DF (no. of failures)	Local ± DF (no. of failures)	Supraclavicular/ Infraclavicular Nodes ± DF (no. of failures)	Axillary Nodes ± DF (no. of failures)	Internal Mammary ± DF (no. of failures)	More Than One Regional Site (no. of failures)	DF Only (no. of failures)	Other* (no. of failures)
I	19.2	491	78	100	49	30	15	2	4	156	27
II	19.4	327	73	95	44	32	6	4	9	153	12
III	19.4	307	57	82	43	23	11	0	5	108	42
IV	19.2	167	28	38	19	8	4	0	7	54	57
V	15.3	2,091	294	378	210	74	52	3	39	618	166
Premenopausal node-negative		692	82	100	59	19	14	2	6	185	38
Postmenopausal node-negative		583	57	67	44	12	5	0	6	144	74
Premenopausal node-positive		475	92	133	68	30	21	0	14	152	20
Postmenopausal node-positive		341	63	78	39	13	12	1	13	137	34
VI	10.0	1,042	184	249	137	68	33	1	10	336	19
VII	10.0	927	143	196	100	65	25	1	5	279	72

Abbreviations: LRF, locoregional failure; DF, distant failure.

*Includes second primary tumors, deaths without recurrence, and 21 deceased patients for whom the site of first recurrence was unknown.

was defined accordingly. The highest risk corresponded to larger tumors with VI (Table 3). Table 4 shows that the 10-year CIF estimates for such patients in the very high–risk group were 15%, 19%, and 27% for the three event types LRF only, LRF ± DF, and DF only, respectively. Compared with the low-risk group, these estimates were approximately a 2.5-fold increase for LRF and LRF ± DF and 59% higher for DF. Figure 1 shows the CIF estimates of LRF ± DF for the three risk groups.

The 10-year CIF estimates for LRF ± DF according to randomized treatment were 12% (SE = 2%) for the PeCMF group (n = 457) and 18% (SE = 3%) for the no adjuvant therapy group (n = 235; $P = .035$).

Postmenopausal Patients With Node-Negative Disease

Only two risk groups could be defined for this cohort of patients on the basis of the information obtained from the multivariate model. VI was the only factor that significantly predicted outcome. The low-risk/medium-risk group corresponded to the absence of VI, whereas the high-risk/very high–risk group corresponded to the presence of VI (Table 3). The overall P value for VI was .006. Table 4 shows that the 10-year CIF estimates for the high-risk/very high risk–group were 14%, 16%, and 23% for the three event types LRF only, LRF ± DF, and DF only, respectively. These corresponded to at least two-fold increases from the estimates for the low-risk/medium-risk group for LRF and LRF ± DF, but only to a 21% increase in CIF for DF. Figure 2 shows the CIF curves for LRF ± DF for the two risk groups.

The 10-year CIF estimates for LRF ± DF according to randomized treatment were 10% (SE = 2%) for the PeCMF group (n = 391) and 14% (SE = 3%) for the no adjuvant therapy group (n = 192; $P = .18$).

Table 3. Risk Group Definitions (With Respect to Locoregional Failure ± Distant Failure)

Premenopausal, Node-Negative Patients (n = 692)				
	TumorSize≤2cm		TumorSize>2cm	
VI, no	Low (206)		Medium/high (145)	
VI, yes	Medium/high (149)		Very high (122)	
	Postmenopausal, Node-Negative Patients (n = 583)			
VI, no	Low/medium (322)			
VI, yes	High/very high (225)			
	Premenopausal, Node-Positive Patients (n = 2335)			
	1-3 Nodes		4+ Nodes	
	VI, No	VI, Yes	VI, No	VI, Yes
Grade 1	Low (98)	Low (91)	Medium (57)	High (43)
Grade 2	Low (219)	Medium (267)	High (123)	Very high (214)
Grade 3	Low (145)	High (219)	High (67)	Very high (216)
	Postmenopausal, Node-Positive Patients (n = 1742)			
	1-3 Nodes		4+ Nodes	
	T ≤ 2 cm	T > 2 cm	T ≤ 2 cm	T > 2 cm
Grade 1	Low (95)	Low (66)	High (24)	High (39)
Grade 2	Low (166)	Medium (202)	High (94)	Very high (182)
Grade 3	Medium (65)	High (151)	Very high (50)	Very high (153)

NOTE. Numbers in parentheses are the number of patients in each category (patients with missing covariates not shown).

Abbreviation: VI, vessel invasion; T, tumor size.

Premenopausal Patients With Node-Positive Disease

The number of positive nodes ($P < .001$), VI ($P < .001$), and grade ($P < .001$) were important prognostic factors determined in the regression models. The presence of VI produced an increase in the risk of LRF ± DF, as did the presence of a large number of positive nodes and a higher tumor grade. Because of the presence of three statistically significant risk factors in this patient population, each risk group corresponded to several different combinations of covariate values (Table 3). The estimated 10-year CIFs for the very high–risk group for LRF, LRF ± DF, and DF were 25%, 35%, and 41%, respectively. These corresponded to increases from the low-risk group estimates of approximately 2.5 times for LRF and LRF ± DF and of approximately 80% for DF (Table 4). Figure 3 shows the complete CIF estimated for LRF ± DF events for the four risk groups.

Postmenopausal Patients With Node-Positive Disease

The analysis for this patient population revealed the presence of three significant prognostic factors: tumor size ($P = .036$), the number of positive nodes ($P < .001$), and tumor grade ($P = .011$). A large number of positive lymph nodes, a high tumor grade, and a large tumor size all contributed to a higher risk for LRF ± DF (Table 3). Table 4 shows that the 10-year CIF estimates for LRF, LRF ± DF, and DF events corresponding to

Table 4. Ten-Year Cumulative Incidence Estimates and Overall Survival Estimates

Risk Group*	LRF		LRF ± DF		DF		OS	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Premenopausal, node-negative patients								
Low	0.06	0.02	0.08	0.02	0.17	0.03	0.83	0.03
Medium/high	0.13	0.02	0.15	0.02	0.25	0.03	0.75	0.03
Very high	0.15	0.03	0.19	0.03	0.27	0.04	0.68	0.04
Postmenopausal, node-negative patients								
Low/medium	0.06	0.01	0.08	0.02	0.19	0.02	0.82	0.02
High/very high	0.14	0.02	0.16	0.02	0.23	0.03	0.68	0.03
Premenopausal, node-positive patients								
Low	0.10	0.01	0.14	0.02	0.23	0.02	0.77	0.02
Medium	0.15	0.02	0.19	0.02	0.26	0.02	0.68	0.02
High	0.20	0.02	0.27	0.02	0.37	0.02	0.48	0.02
Very high	0.25	0.02	0.35	0.02	0.41	0.02	0.34	0.02
Postmenopausal, node-positive patients								
Low	0.13	0.02	0.14	0.02	0.23	0.02	0.67	0.02
Medium	0.14	0.02	0.18	0.02	0.29	0.02	0.56	0.03
High	0.17	0.02	0.24	0.02	0.35	0.02	0.46	0.02
Very high	0.23	0.02	0.34	0.02	0.40	0.03	0.30	0.02

Abbreviations: LRF, locoregional failure; DF, distant failure; OS, overall survival.

*Note that the definition of the risk groups changes across the patient populations (see text).

the very high–risk group were 23%, 34%, and 40%, respectively. These corresponded to an 80% increase and to a 2.4-fold increase from the low risk levels for LRF and LRF ± DF, respectively, and to a 74% increase in CIF for DF events. Figure 4 shows the estimated CIF curves for LRF ± DF for the four risk groups.

10-Year LRF ± DF Estimates

Table 5 reports the 10-year cumulative incidence estimates of LRF ± DF events within patient subgroups defined with respect to number of positive nodes (zero, one to three, four to nine, or 10 or more), tumor size (≤ 2 cm, > 2 cm to ≤ 5 cm, or > 5 cm), VI (yes or no), and grade (1, 2, or 3). These are presented to provide comparison to data presented from other series on this subject.[31,32]

DISCUSSION

Our study was based on more than 4,000 breast cancer patients with axillary lymph node involvement, all of whom were treated with adjuvant cytotoxic and/or endocrine systemic therapy after a mastectomy without postoperative radiotherapy in seven successive clinical trials of the IBCSG. In addition, we included more than 1,200 patients with axillary lymph node–negative disease who received either surgery alone or one course of adjuvant cytotoxic therapy to identify features that predict an increased risk of local and regional relapse even in a population considered, on average, to be at low risk for such breast cancer–related events. Therefore, we were able to identify risk factors for LRF for four clinically oriented patient cohorts on the basis of menopausal status and nodal involvement. We used CIF

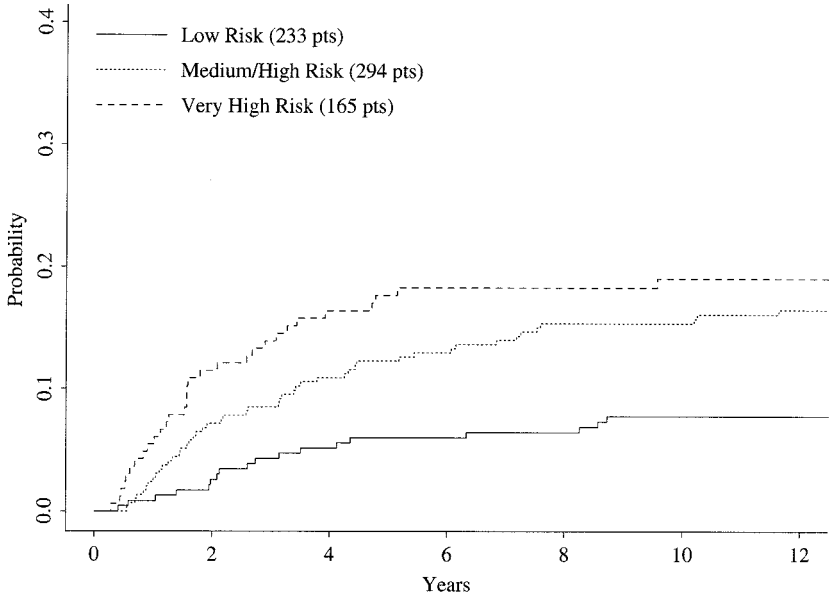

Fig 1. Cumulative incidence functions for locoregional failure ± distant failure according to risk group for premenopausal patients with node-negative disease. pts, patients.

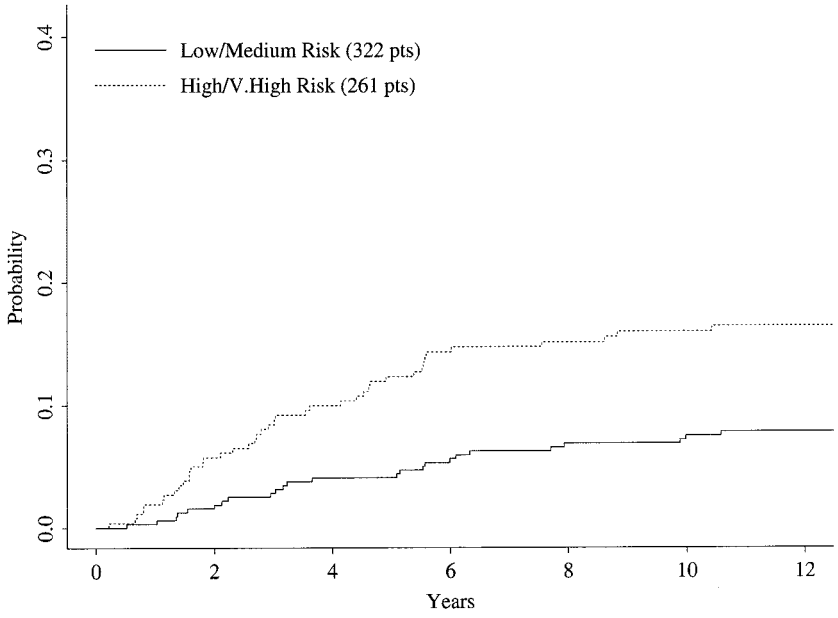

Fig 2. Cumulative incidence functions for locoregional failure ± distant failure according to risk group for postmenopausal patients with node-negative disease. Patients with missing vessel invasion information are not shown. pts, patients.

regression analysis to define risk groups for LRF within each of the four cohorts. This approach is similar in spirit to the determination of risk groups using the Cox model, as it also uses regression models (in our case for the cumulative incidence function) to define a risk index, which is then used to identify groups at increasing risk of LRF ± DF events. It should be noted that for the four different data sets, the definitions of the risk groups are based on different models, and thus such risk groups cannot be properly compared across patient cohorts. For such a comparison, we recommend examination of the CIF estimates.

In patients without axillary lymph node involvement, VI (pre- or postmenopausal patients) and tumor size greater than 2 cm (premenopausal patients only) defined risk groups. In the premenopausal cohort, a low risk of 8% LRF ± DF at 10 years was found if the size of the tumor was ≤ 2 cm and there was no VI, and a very high risk of 19% was found if the size of the tumor was greater than 2 cm and VI was present. For postmenopausal women, those with tumor size greater than 2 cm had a 10-year CIF of 16% for LRF ± DF. Thus size of tumor and VI might define a group of patients with axillary node–negative disease who have a risk of LRF close to the 20% suggested as a reasonable level to indicate postoperative radiation therapy.[14]

Overall, results according to randomized treatment showed a reduction in LRF ± DF for patients with node-negative disease who received the single cycle of PeCMF compared with those who received no adjuvant therapy. Additional study is required, however, to determine how much the risk of LRF is reduced by adequate adjuvant systemic therapy selected according to the endocrine responsiveness of the primary tumor.[14]

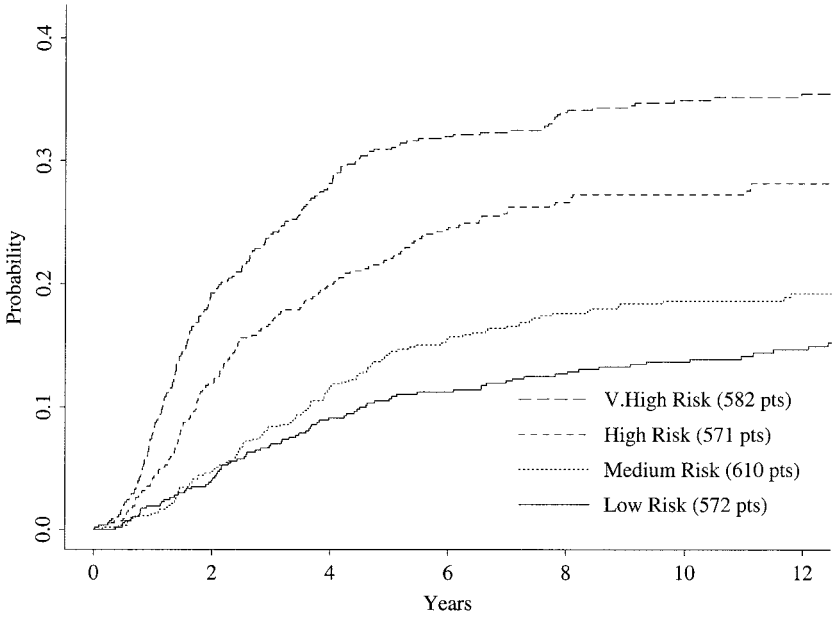

Fig 3. Cumulative incidence functions for locoregional failure ± distant failure according to risk group for premenopausal patients with node-positive disease. pts, patients.

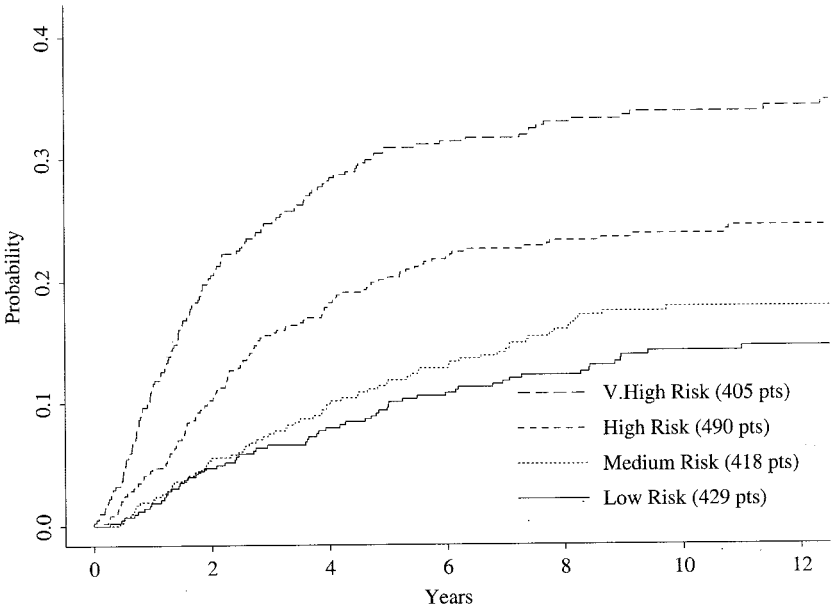

Fig 4. Cumulative incidence functions for locoregional failure ± distant failure according to risk group for postmenopausal patients with node-positive disease. pts, patients.

For patients with lymph node metastases, the number of involved nodes and histologic grade were predictors of LRF for both pre- and postmenopausal women. VI provided supplementary prognostic information for premenopausal patients, and size of tumor provided supplementary prognostic information for postmenopausal women. Generally, patients with four or more involved nodes had high (ie, ≥ 24%) or very high (approximately 35%) cumulative risk of LRF at 10 years. Among patients with one to three involved nodes, premenopausal patients with histologic grade 3 tumors with VI and postmenopausal women with grade 3 tumors greater than 2 cm also belonged to the high-risk group. This reinforces the importance of accurate pathologic evaluation of the specimen.

We previously reported that the 10-year LRF ± DF cumulative incidence was 18% for 2,108 patients with node-positive disease in IBCSG trials I though V who received more effective adjuvant systemic therapy compared with 36% for 722 patients who received less effective treatment.[15] It is possible that even more effective adjuvant systemic therapy selected according to the endocrine responsiveness of the primary tumor[14] might further reduce the risk of LRF.

There is currently a general consensus that postoperative radiotherapy should be given to certain groups of patients with breast cancer who receive adjuvant systemic treatment not only with the aim of reducing the risk of LRF of the disease, but also to improve breast cancer survival.[10-14] This applies to the group of patients with four or more lymph node metastases, but there is a lack of consistent knowledge concerning the impact of other factors as predictors of a clinical benefit from postoperative radiotherapy.[11]

The overviews of radiotherapy trials show similar proportional reductions of locoregional relapses in different treatment groups, but absolute differences rather than relative differences should guide treatment decisions. Therefore, this retrospective study was performed to investigate the absolute rates of LRF in different patient groups according to several patient- and tumor-related factors. Because all patients were enrolled onto IBCSG studies, selection was according to defined inclusion criteria of the trials and does not represent a random sample of all postmastectomy cases. On the other hand, the selection process included quality control of diagnostic and surgical procedures, standards for adjuvant treatment, follow-up procedures, and results reporting. Only patients with radically removed tumors without involvement of skin or fascia were included in the IBCSG trials, and most of the studies required a minimum of eight lymph nodes examined for the inclusion of patients. The number of lymph nodes removed has been found in some studies to be of prognostic importance for LRF, possibly as a result of understaging and perhaps of undertreatment of the axilla.[31] It has been suggested that the high frequency of LRF of some clinical trials[5-7] might in fact result from less optimal surgical techniques, which also results in few retrieved lymph nodes.[8]

Two recently published retrospective series explored various factors of prognostic importance for LRF in more than 1,000 patients.[31-33] The study by Recht et al[31] was based on approximately 2,000 patients who had been treated with mastectomy and postoperative adjuvant chemotherapy within four Eastern Cooperative Oncology Group studies. Number of lymph node metastases, number of examined nodes, tumor size, estrogen receptor protein, menopausal status, and age of the patients were analyzed, and rates were based on CIFs. In a multivariate setting, number of involved nodes, tumor size, and estrogen receptor status, but also the number of examined nodes, significantly contributed to LRF.

Katz et al[32,33] investigated approximately 1,000 patients who had been included in prospective clinical trials at the M.D. Anderson Cancer Center. The patients were all treated with a modified radical mastectomy and received adjuvant anthracycline-containing chemotherapy but without radiotherapy. Subjects were selected from a cohort of 1,800 patients, some of whom had received radiotherapy "at the discretion of the treating oncologist." The effect of this selection on the results is unclear. The first report focused on clinical features,[32] and the second

Table 5. Ten-Year LRF ± DF Cumulative Incidence Function (CIF) Estimates, SEs, Number of LRF ± DF Events, and Total Number of Patients According to Menopausal Status, Number of Involved Lymph Nodes, Tumor Size, Vascular Invasion, and Grade

	Premenopausal Patients												Postmenopausal Patients											
	No. of Involved Nodes												No. of Involved Nodes											
	0			1-3			4-9			10+			0			1-3			4-9			10+		
T stage	CIF (%)	SE	LRF ± DF/ PTS	CIF (%)	SE	LRF ± DF/ PTS	CIF (%)	SE	LRF ± DF/ PTS	CIF (%)	SE	LRF ± DF/ PTS	CIF (%)	SE	LRF ± DF/ PTS	CIF (%)	SE	LRF ± DF/ PTS	CIF (%)	SE	LRF ± DF/ PTS	CIF (%)	SE	LRF ± DF/ PTS
Overall																								
pT1	11	2	41/365	16	2	102/585	29	3	55/190	30	6	21/69	10	2	33/321	13	2	56/428	26	4	45/159	26	6	18/62
pT2	17	2	45/256	20	2	148/710	28	2	112/381	41	4	68/163	13	2	30/223	19	2	98/527	29	3	85/296	34	4	48/135
pT3	30	11	6/20	25	6	17/61	33	6	19/57	35	8	14/40	14	15	1/7	16	*7*	*5*/31	35	*7*	16/43	*48*	*10*	*11/23*
No VI																								
pT1	6	2	13/206	12	2	31/249	26	6	16/63	27	10	6/22	*7*	2	15/210	12	2	24/199	25	6	14/49	13	9	2/16
pT2	14	3	21/134	16	2	50/290	19	4	25/125	43	*7*	21/47	9	3	9/101	20	3	46/241	23	4	25/109	35	9	13/34
pT3	24	14	3/11	20	9	6/20	30	10	*7*/23	11	12	1/9	0	0	0/2	14	8	3/21	53	13	10/17	*50*	*35*	*1/2*
VI																								
pT1	16	3	26/149	20	3	60/260	31	*5*	30/93	27	*7*	11/41	16	4	16/101	15	3	25/170	32	*5*	28/83	36	8	15/37
pT2	20	4	23/114	22	2	78/329	33	3	73/209	42	*5*	44/104	16	4	19/113	18	3	36/208	33	4	47/143	34	*5*	30/86
pT3	25	17	2/8	32	8	11/35	39	10	11/28	41	10	11/27	25	26	1/4	13	13	1/8	24	10	*5*/21	*47*	*11*	*9/19*
Grade 1																								
pT1	6	3	4/63	*5*	2	9/100	19	*7*	8/38	13	13	1/8	4	2	4/82	12	3	11/95	0	0	2/21	33	33	2/3
pT2	6	6	2/18	17	4	15/82	21	*7*	8/38	*50*	23	3/6	*7*	*5*	2/30	20	*5*	12/63	14	*7*	4/29	0	0	2/3
pT3	0	0	0/1	25	17	3/8	*29*	*17*	*2/7*	0	0	0/2	—		0/0	*100*	*0*	3/3	14	14	2/7	—		0/0
Grade 2																								
pT1	13	3	26/182	15	2	38/227	32	6	20/63	21	8	6/28	15	3	21/144	13	3	22/166	31	6	20/61	31	8	11/33
pT2	17	4	17/93	18	3	49/241	24	4	36/131	34	6	25/71	14	4	11/80	19	3	36/188	28	*5*	30/104	31	6	17/*55*
pT3	0	0	0/4	27	10	*7*/22	30	8	10/33	24	11	4/17	33	37	1/3	0	0	0/14	29	12	*5/17*	*33*	*19*	*2/6*
Grade 3																								
pT1	9	3	9/100	24	4	33/140	31	*7*	13/42	32	10	*7*/22	8	3	6/80	17	*5*	11/*65*	41	8	17/39	27	15	3/11
pT2	19	4	24/125	22	3	49/213	34	4	44/131	*47*	*7*	29/62	15	4	16/104	21	3	30/144	31	*5*	26/84	44	*7*	22/50
pT3	*50*	17	*5*/10	30	11	6/20	60	17	6/10	41	13	*7*/17	0	0	0/3	14	14	*1/7*	44	18	*4/9*	*60*	*15*	*6/10*

Abbreviations: LRF, locoregional failure; DF, distant failure; PTS, patients; VI, vessel invasion; pT, pathologic tumor (stage).

NOTE. Italicized numbers denote cells for which no patients have been followed for at least 10 years.

report focused on tumor-related factors obtained from the pathology reports of the M.D. Anderson review before treatment.[33] Ten-year Kaplan-Meier estimates of LRF with or without prior or simultaneous distant metastases were studied. A multivariate Cox regression analysis revealed that the presence of four or more involved nodes, tumor size greater than 5 cm, close or positive surgical margins, or clinically or gross pathologically multicentric disease, but not the presence of lymph-vascular space invasion, was an independent predictor of LRF. Presence of lymph-vascular space invasion, however, was a significant predictor in the univariate analysis. A separate analysis was performed for patients with one to three involved nodes. In the multivariate analysis, tumor size, invasion of skin or nipple, and the presence of close or positive margins were predictors of LRF. It is thus noteworthy that in addition to the number of involved nodes and size of tumor, multicentric disease, defined as two or more areas of tumor in different quadrants or separated by at least 4 cm, invasion in skin or nipple, or close or positive surgical margins predicted a high rate of LRF. Because of the restricted entrance criteria for patients in the IBCSG trials, few patients, if any, in our study had positive margins.

It is difficult to compare the frequencies of LRF among different studies. The selection and the treatment of patients vary, as well as the definition of LRF. In some studies only local relapses (ie, on the chest wall) are scored as LRF; supraclavicular nodes are sometimes counted as DFs and sometimes as LRFs. In our study as well as those of Recht et al[31] and Katz et al,[32] relapses on the chest wall and in the axilla, supra- or infraclavicular fossae, and internal mammary nodes were scored as LRFs. Statistics may be based on a first appearance of LRF without or with coincident DF or on LRF appearing at any time. In our study, figures are given for LRFs appearing either alone or with DF as a first event, and the statistical considerations are based on LRF as a first event with or without DF. The reporting of LRF after a known DF is considered to be unreliable. The length of follow-up as well as the statistical techniques used certainly influences the reported rate of LRF.

In our analysis, we used the CIFs to estimate the risk of the events of interest.[29] The CIF is a function that for each failure type describes the probability that an individual has had a failure of that type before a given time point in the presence of competing types of failure. This is different from the study of the so-called cause-specific hazard of having a failure of a specific type, where the hazard is defined by considering all competing failures as censored observations, and the Kaplan-Meier method is used to produce probability estimates.[30] In the context of competing risks of failure, the Kaplan-Meier estimates are always higher than the CIF estimates and always overestimate the chance that patients will actually suffer an LRF, because the Kaplan-Meier probabilities estimate the incidence only if all other competing causes of failure cannot occur.[34,35] CIF estimates were also used for the analysis by Recht et al,[31] but Katz et al[32,33] used Kaplan-Meier estimates. A reanalysis of the Katz et al data using CIF methodology would provide better estimates

for the true incidence of LRF because all patients in their series received anthracycline-containing chemotherapy and, therefore, were probably at higher risk for distant relapse as site of first failure. The overestimation of LRF incidence by the Kaplan-Meier method increases as the risk of DF-only events increases.[34,35]

We have shown that local and regional relapses constitute a therapeutic problem in breast cancer despite controlled surgery and adjuvant cytotoxic and/or endocrine treatment. Available studies consistently show that an increasing number of involved axillary lymph nodes also increases the risk of such failures and that the size of the tumor adds to the risk. Especially among women with one to three involved nodes enrolled in ongoing trials of postoperative radiotherapy, there is a need to explore other possible predictors of recurrence, including histologic grade and VI as identified in our study.

ACKNOWLEDGMENT AND APPENDIX

The acknowledgment and appendix are available online at www.jco.org.

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