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ORIGINAL REPORT

Distinct Clinical and Prognostic Features of Infiltrating Lobular Carcinoma of the Breast: Combined Results of 15 International Breast Cancer Study Group Clinical Trials

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A B S T R A C T

Purpose
To determine how patients with infiltrating lobular carcinoma (ILC) differ from patients with the more common infiltrating ductal carcinoma (IDC) with regard to patient and tumor factors, local treatment, and patterns of recurrence.

Patients and Methods
Twelve thousand two hundred six breast cancer patients entered onto 15 International Breast Cancer Study Group trials between 1978 and 2002 were categorized as having ILC, IDC, or other/mixed types.

Results
Seven hundred sixty-seven tumors (6.2%) were classified as ILC, 8,607 (70.5%) were classified as IDC, and 2,832 (23.2%) were classified as other. The analysis is limited to the 9,374 patients categorized as either pure IDC or ILC. The median follow-up time was 13 years. Compared with IDC, ILC was associated with older age; larger, better differentiated, and estrogen receptor (ER)–positive tumors; and less vessel invasion. Mastectomy was used more frequently for ILC ($P < .01$). There was a significant ($P < .01$) early advantage in disease-free survival and overall survival for the ILC cohort followed by a significant ($P < .01$) late advantage for the IDC cohort after 6 and 10 years, respectively. Similar patterns were observed in cohorts defined by ER status. ILC was associated with an increased incidence of bone events but a decrease in regional and lung events (all $P < .01$).

Conclusion
ILC is more than a histologic variant of breast cancer. The diagnosis of ILC carries distinct prognostic and biologic implications.

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INTRODUCTION

Infiltrating lobular carcinoma (ILC) and infiltrating ductal carcinoma (IDC) are the two most common histologic types of invasive breast cancer, with IDC occurring in approximately three fourths of patients and ILC occurring in less than one tenth of patients.[1-6] As such, most clinical research conclusions are driven by the outcome of patients with IDC, which dominates the breast cancer population. ILC differs from IDC in its increased frequency of multifocality and bilaterality, the difficulty in defining its margins at clinical examinations, its mammographic features, and even its features at surgery.[3-5,7] Other distinguishing features of ILC are less certain, including its relationship with endocrine responsiveness and whether patterns of recurrence and/or overall prognosis are different from IDC. Most available data on ILC are derived from retrospective series, be they from single centers or population-based studies.[2-6,8] Therefore, we have carried out a detailed study of the prognostic features of ILC versus IDC by analyzing baseline patient and tumor factors, local treatments, risk of contralateral breast cancer, and local, regional, and distant recurrence patterns of patients entered onto 15 prospective adjuvant treatment trials of the International Breast Cancer Study Group (IBCSG).

PATIENTS AND METHODS

We analyzed data from 13,220 patients with early breast cancer who were entered onto IBCSG (formerly the Ludwig Breast Cancer Study Group) Trials I through 15-95[9-20] between 1978 and 2002 (Appendix Table A1, online only).

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The trial patients were carefully followed annually for survival and disease status, including sites of first and subsequent recurrence. Informed consent was required according to the criteria established within individual countries. The trial protocols were reviewed and approved by local institutional review boards.

Pathology Assessment

The histologic type was determined by central pathology review of a stained hematoxylin and eosin slide for 13 of the 15 trials and by local assessment for two trials (VI and VII). Tumors classified as ILC had no invasive histologic types reported other than invasive lobular carcinoma. Likewise, IDC had only invasive ductal carcinoma. All other tumors were classified as other, including mixed IDC/ILC. The 1,014 patients (7.6%) with unknown histologic type (not performed, not recorded, or not assessable) are excluded from the analysis. Tumor size, grade, vessel invasion, and estrogen receptor (ER) status are all based on the local assessments. ER determination for these trials was by extraction assay, and immunohistochemical methods were allowed as they became available. ER negative was defined as less than 10 fmol/mg cytosol protein, and for immunohistochemistry, negative and positive were reported as defined locally.

Statistical Methods

Disease-free survival (DFS) was defined as the length of time from the date of random assignment to any relapse (including ipsilateral breast recurrence), the appearance of a second primary cancer (including contralateral breast cancer), or death, whichever occurred first. Overall survival (OS) was defined as the length of time from the date of random assignment to death from any cause. Survival curves were estimated using the Kaplan-Meier method.[21] Nonproportional hazards between histologic types for both DFS and OS were modeled assuming proportional hazards in a series of consecutive time intervals using a piecewise Cox regression model.[22] We report model estimates of relative risk, always comparing ILC with IDC, with their corresponding 95% CIs. Baseline factors included in multiple regression analyses were nodal status (node positive or node negative), vessel invasion (yes or no), pathologic tumor size ($\leq$ 2 cm, $>$ 2 cm, or unknown), tumor grade (1, 2, 3, or unknown), ER status (ER negative, ER positive, or ER unknown), menopausal status (premenopausal or postmenopausal), age ($>$ 50 or $\leq$ 50 years), and adjuvant systemic therapy regimen.

Cumulative incidence functions for competing sites of recurrence were estimated.[23] These functions estimate the actual percentage of patients who will experience the various competing events within the study cohorts as opposed to the overestimated percentages obtained with the Kaplan-Meier method based on the cause-specific hazards.[24,25] Differences between the cumulative incidence functions according to histology type (ILC or IDC) were tested for statistical significance using the procedure of Gray.[26] A cumulative incidence function regression model of Fine and Gray[27] was used for multiple regression analyses.

Associations between categoric variables and the histologic type were assessed using a χ^2 test. No statistical adjustment was made for performing multiple tests. *P* values are two-sided.

Categories of Sites of Recurrence

Breast cancer recurrences were classified according to site as follows: local, confined to the ipsilateral breast or chest wall and including mastectomy scars; regional, including ipsilateral axillary, supraclavicular, and internal mammary lymph node metastases; distant soft tissue, nodes, or bone marrow; bone; and viscera, including all other organ involvement and diffuse intra-abdominal metastases. Other events, including contralateral breast cancer, nonbreast second malignancies, and deaths without prior malignancies, were also recorded. Time to first event was defined as time from random assignment to the occurrence of a first event of any type. An event was considered to be a component of a first event if diagnosed within a 2-month time frame. Occurrences of a first event, with or without recurrence at any other site, were the events of interest. All other sites of first event and any other events, such as, contralateral breast cancer, nonbreast second malignancies, and death without prior cancer event, were considered competing events.

RESULTS

Association With Tumor and Patient Factors

Histologic type was available for 12,206 patients; 767 (6.2%) were classified as ILC, 8,607 (70.5%) were classified as IDC, and the remainder were classified as other and/or mixed types. The proportion of patients classified as ILC ranged from 1.3% to 9.5% across the 15 trials, and the proportion of patients categorized as IDC ranged from 67.1% to 74.2% (Appendix Table A2, online only). Trials VI and VII, in which histopathology material was not centrally reviewed, had a slightly higher proportion of ILC compared with the other trials (7.9% and 9.5%, respectively).

The remainder of this analysis is based on the 9,374 patients categorized as ILC or IDC. Table 1 lists the proportions of ILC and IDC according to baseline features. Compared with patients with IDC, patients with ILC were older and presented more frequently with ER-positive tumors and with tumors greater than 2 cm. Patients with IDC presented more frequently with grade 3 tumors and vessel invasion. Differences according to nodal status, treatment group, and menopausal status were not statistically significant.

Local Treatment

Mastectomy was used more frequently than breast-conserving surgery within the ILC cohort (404 of 563 patients; 71.7%) compared with the IDC cohort (3,310 of 5,889 patients; 56.2%; $P < .01$; Table 1). It should be noted that the protocols included requirements with regard to local treatment. Patients enrolled onto trials I through V all received a mastectomy and, therefore, are excluded from the local treatment section in Table 1. Because most of the trials did not allow radiotherapy after mastectomy, this modality was used infrequently (2.2%) and with similar frequency within both cohorts ($P = .78$). All of the trials except for two required radiotherapy after breast-conserving surgery. Of the 2,579 patients in the IDC cohort who received a breast-conserving procedure, 2,312 (89.6%) received radiotherapy; 83.6% of patients (133 of 159 patients) in the ILC cohort received radiotherapy ($P = .02$).

DFS and OS

The DFS curve (Fig 1A) shows an early advantage for the ILC cohort, but after 6 years, an advantage emerges for the IDC cohort. Similarly, the OS curve (Fig 1B) shows an early advantage for the ILC cohort, whereas after 10 years, we see an advantage for the IDC cohort. There was a statistically significant time-dependent effect of histologic type for DFS and OS (both $P < .01$), implying that the effect of histologic type varies across time. On the basis of Figures 1A and 1B, a piecewise Cox regression model was estimated for various change points within the time interval of 6 to 8 years. Although the results were stable for various change points within this chosen range, the change point at 6 years provided the best model fit for the DFS analysis. Within the first 6 years, the risk of a DFS event for patients with ILC was 16% lower compared with patients with IDC (hazard ratio [HR] = 0.84; 95% CI, 0.74 to 0.95; $P < .01$; Table 2). After 6 years, the risk of a DFS event was 54% higher for the ILC cohort compared with the IDC cohort (HR = 1.54; 95% CI, 1.31 to 1.81; $P < .01$; Table 2). No two-way interaction effects between the baseline factors

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Table 1. Proportion of Infiltrating Ductal and Infiltrating Lobular Histologic Types According to Baseline Characteristics and Treatment

Factor	Histopathology: Infiltrating Ductal, No. of Patients (n = 8,607)	Infiltrating Ductal, %	Infiltrating Lobular, No. of Patients (n = 767)	Infiltrating Lobular, %	Total, No. of Patients (N = 9,374)	Total, %	P*
Age, years							.02
> 50	4,731	54.9	454	59.1	5,185	55.3	
≤ 50	3,876	45.0	313	40.8	4,189	44.6	
Nodal status							.20†
0	2,677	31.1	214	27.9	2,891	30.8	
1-3	3,411	39.6	314	40.9	3,725	39.7	
4+	2,388	27.7	220	28.6	2,608	27.8	
Trial 10 Nx	131	1.5	19	2.4	150	1.6	
Tumor grade							< .01
1	1,116	12.9	143	18.6	1,259	13.4	
2	3,766	43.7	448	58.4	4,214	44.9	
3	3,595	41.7	90	11.7	3,685	39.3	
Unknown	130	1.5	86	11.2	216	2.3	
ER status							< .01
Negative	2,719	31.5	133	17.3	2,852	30.4	
Positive	5,123	59.5	586	76.4	5,709	60.9	
Unknown	765	8.8	48	6.2	813	8.6	
Tumor size							< .01
0-2 cm	4,127	47.9	322	41.9	4,449	47.4	
> 2 cm	4,358	50.6	423	55.1	4,781	51.0	
Unknown	122	1.4	22	2.8	144	1.5	
Vessel invasion							< .01
No	4,268	49.5	511	66.6	4,779	50.9	
Yes	3,181	36.9	147	19.1	3,328	35.5	
Unknown	1,158	13.4	109	14.2	1,267	13.5	
Menopausal status							.34
Premenopausal	4,205	48.8	361	47.0	4,566	48.7	
Postmenopausal	4,402	51.1	406	52.9	4,808	51.2	
Randomly assigned treatment							.19
No adjuvant therapy	503	5.8	31	4.0	534	5.6	
ET alone	1,594	18.5	138	17.9	1,732	18.4	
ET + CT	3,314	38.5	299	38.9	3,613	38.5	
CT alone	3,196	37.1	299	38.9	3,495	37.2	
Local treatment‡							
Mastectomy	3,310	56.2	404	71.7	3,714	57.5	< .01
BC	2,579	43.7	159	28.2	2,738	42.4	
Mastectomy and no RT	3,180	53.9	387	68.7	3,567	55.2	.78
Mastectomy with RT	130	2.2	17	3.0	147	2.2	
BC and no RT	267	4.5	26	4.6	293	4.5	.02
BC with RT	2,312	39.2	133	23.6	2,445	37.8	

Abbreviations: ER, estrogen receptor; ET, endocrine therapy; CT, chemotherapy; BC, breast conservation; RT, radiotherapy.
*Statistical tests exclude the unknowns.
†Trial 10 Nx: clinically node-negative patients were categorized as 0 positive nodes for the statistical test.
‡Trials VI through 15 only.

and histologic type were statistically significant for DFS. After adjusting for the baseline factors listed in Patients and Methods, the results were consistent both before (HR = 0.88; 95% CI, 0.76 to 1.02; $P = .09$) and after (HR = 1.63; 95% CI, 1.35 to 1.97; $P < .01$) 6 years.

A similar crossing pattern was seen for OS but with a later change point. Within the first 10 years, the hazard of death for the ILC cohort was 16% lower compared with the IDC cohort (HR = 0.84; 95% CI, 0.73 to 0.96; $P = .01$; Table 2). After 10 years, the risk of a death was 50% higher for the ILC cohort compared with the IDC cohort (HR = 1.50; 95% CI, 1.22 to 1.86; $P < .01$; Table 2). No two-way interaction effects between the baseline factors and histologic type were statistically significant for OS. Although the result did not achieve statistical significance, after controlling for the baseline factors, a similar result was seen during the first 10 years (HR = 0.92; 95% CI, 0.78 to 1.08; $P = .30$), which was significant after 10 years (HR = 1.63; 95% CI, 1.26 to 2.12; $P < .01$). Results within the ER-negative and ER-positive cohorts showed a similar pattern (Figs 1C through 1F; Table 2), although differences are somewhat more pronounced for ER-negative cohorts compared with ER-positive cohorts.

In addition, we performed similar analyses in the following three subpopulations: excluding patients with lobular ER-negative tumors, excluding patients with lobular tumors with vessel invasion, and

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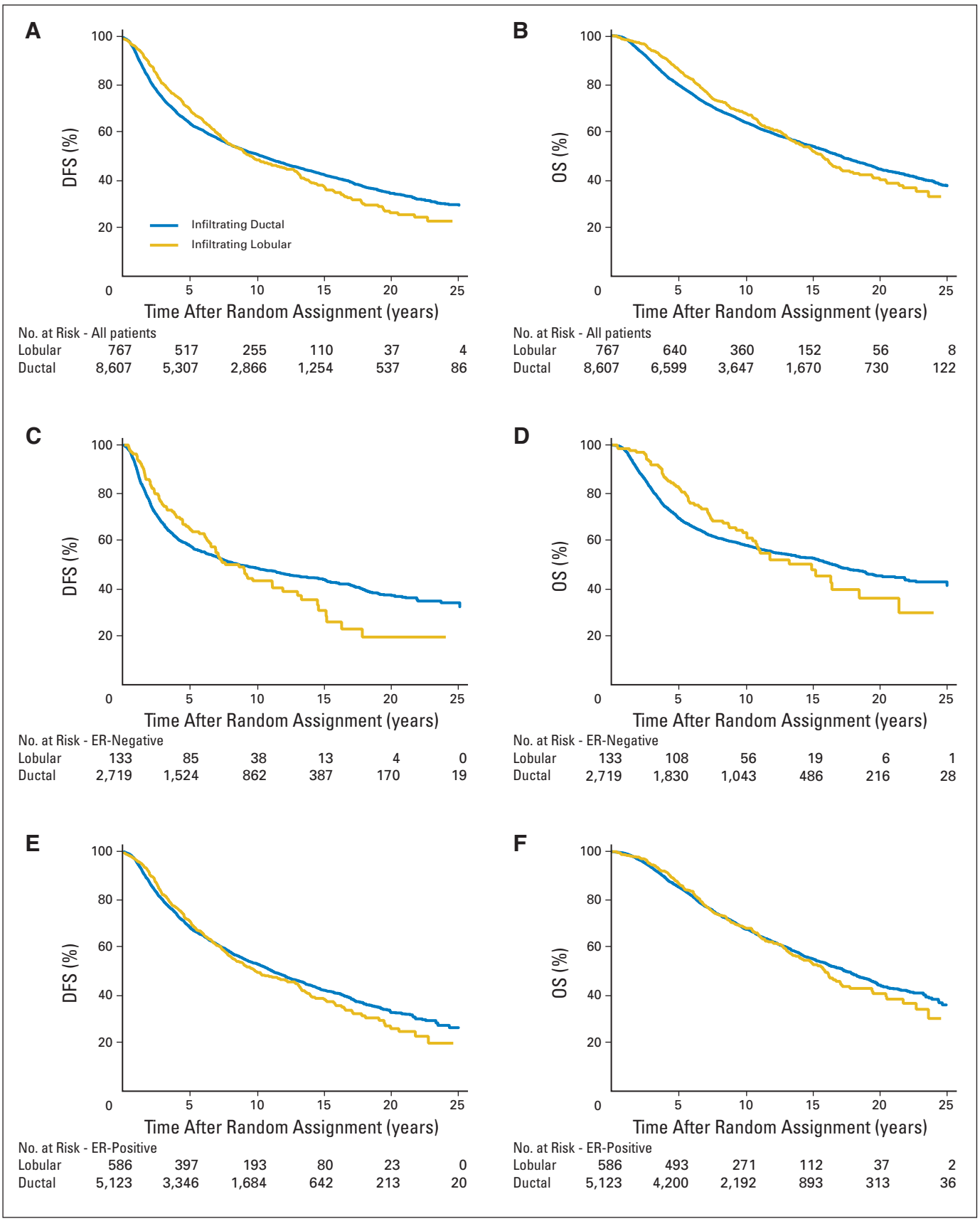

Fig 1. Kaplan-Meier curves of disease-free survival (DFS; left), and overall survival (OS; right) according to histologic type (A and B) in all patients, (C and D) within the estrogen receptor (ER) –negative cohort, and (E and F) within the ER-positive cohort.

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Table 2. Disease-Free and Overall Survival

Histology	No. of Patients	Disease-Free Survival: Total No. of Events	DFS ≤ 6 Years HR	DFS ≤ 6 Years 95% CI	DFS > 6 Years HR	DFS > 6 Years 95% CI	Overall Survival: Total No. of Deaths	OS ≤ 10 Years HR	OS ≤ 10 Years 95% CI	OS > 10 Years HR	OS > 10 Years 95% CI
All patients											
Lobular	767	439	0.84	0.74 to 0.95	1.54	1.31 to 1.81	328	0.84	0.73 to 0.96	1.50	1.22 to 1.86
Ductal	8,607	4,626					3,631				
ER negative											
Lobular	133	83	0.77	0.58 to 1.02	2.80	1.95 to 4.03	62	0.76	0.57 to 1.03	2.69	1.60 to 4.51
Ductal	2,719	1,479					1,229				
ER positive											
Lobular	586	324	0.90	0.78 to 1.04	1.30	1.09 to 1.55	238	0.92	0.79 to 1.07	1.28	1.02 to 1.62
Ductal	5,123	2,624					1,933				

Abbreviations: HR, hazard ratio; ER, estrogen receptor.

excluding patients with lobular tumors that were ER negative or with vessel invasion. The results were similar to those shown in Figure 1 and Table 2 (data not shown).

Sites of First Recurrence

The sites of first DFS event according to histologic type are listed in Table 3. For patients who have received breast-conserving surgery, local recurrences as site of first failure were observed in 8.0% of patients with IDC tumors and 6.3% of patients with ILC tumors. Figure 2 explores the observed differences in local, contralateral, regional, and distant events over time. Incidence over time according to histologic type was similar for local recurrence (Fig 2A). There was no significantly higher incidence of contralateral breast events in our ILC cohort (Fig 2B). We observed a higher incidence of bone events in the ILC cohort (Fig 2E) but a lower incidence of regional (Fig 2C) and lung events (Fig 2F). The pattern of a better outcome for ILC early with a worse outcome later in the follow-up seen in the OS and DFS curves is evident in the incidence over time for any distant recurrence (Fig 2D). The significant differences were retained in the multiple regression analyses (data not shown). The same pattern of cumulative incidence of events shown in Figure 2 is seen within the ER-negative and ER-positive cohorts, as shown in Table 4.

DISCUSSION

ILC is the second most common type of invasive breast cancer after IDC.[1-6,28] In a recent population-based study of 135,157 patients with invasive breast cancer from the Surveillance, Epidemiology, and End Results database of the National Cancer Institute for the period from 1992 to 2001, 76% were IDC, 8% were ILC, 7% were ductal/lobular,

Table 3. Overall Distribution of Infiltrating Ductal and Infiltrating Lobular Histologic Types According to the Site of First Event

First Events	Histopathology: Infiltrating Ductal No. of Patients (n = 8,607)	Infiltrating Ductal %	Infiltrating Lobular No. of Patients (n = 767)	Infiltrating Lobular %	Total No. of Patients (N = 9,374)	Total %
Total events	4,626	53.7	439	57.2	5,065	54.0
Total deaths	3,631	42.2	328	42.8	3,959	42.2
Sites of breast cancer recurrence						
Local	667	7.7	72	9.3	739	7.8
Contralateral breast ± above	322	3.7	38	4.9	360	3.8
Regional ± above	513	5.9	15	1.9	528	5.6
Distant ± above	2,359	27.4	238	31.0	2,597	27.7
Distant: soft tissue, nodes ± above	129	1.4	11	1.4	140	1.4
Distant: bone ± above	899	10.4	120	15.6	1,019	10.8
Distant: viscera ± above	1,331	15.4	107	13.9	1,438	15.3
Bone marrow	21	0.2	5	0.6	26	0.2
Lung	611	7.0	13	1.6	624	6.6
Liver	486	5.6	34	4.4	520	5.5
CNS	139	1.6	9	1.1	148	1.5
Other	322	3.7	57	7.4	379	4.0
Second nonbreast malignancy	355	4.1	35	4.5	390	4.1
Death without prior cancer event	372	4.3	38	4.9	410	4.3
Unknown site	38	0.4	3	0.3	41	0.4

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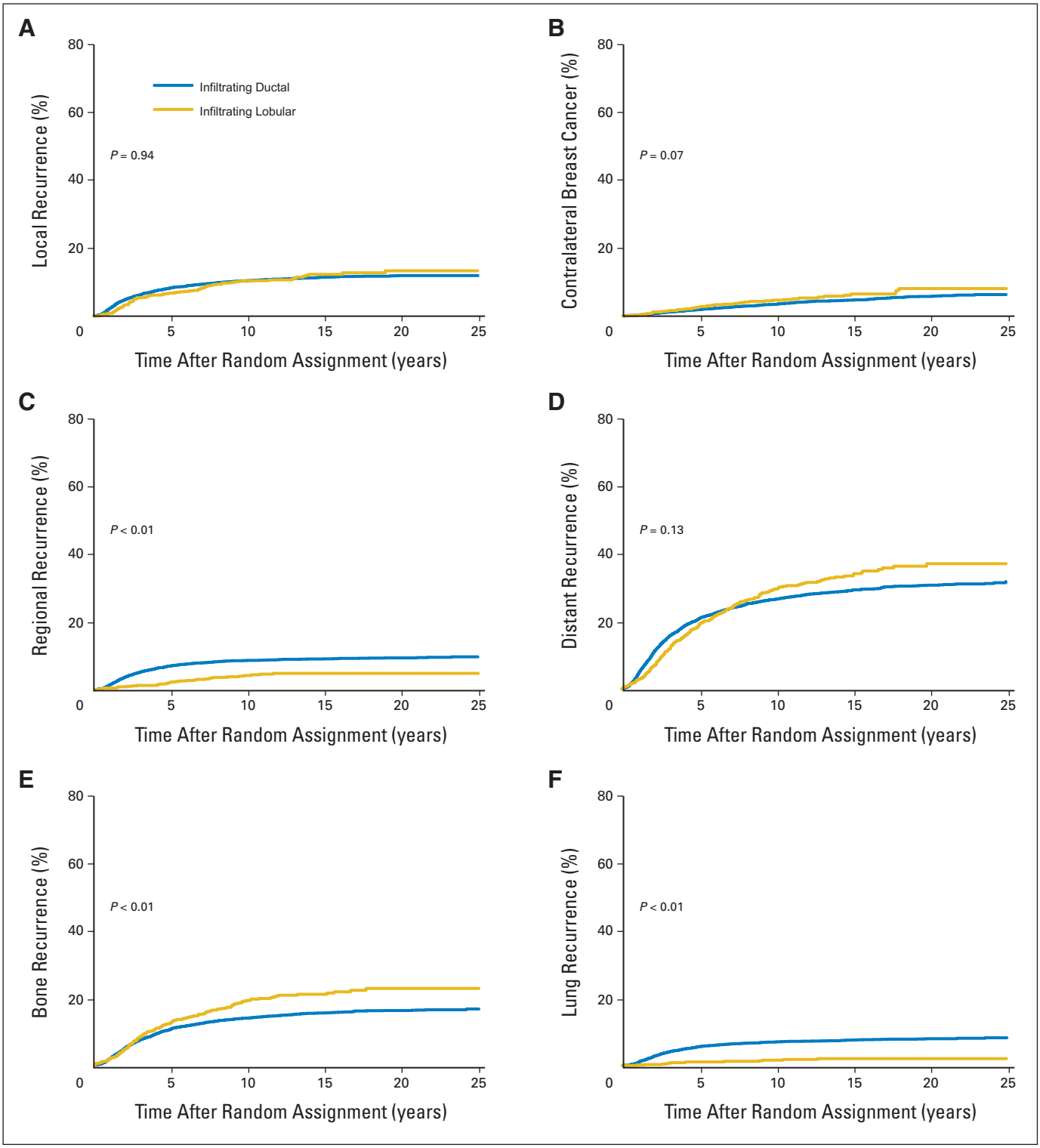

Fig 2. Site-specific cumulative incidence of (A) local recurrence, (B) contralateral breast cancer, (C) regional recurrence, (D) distant recurrence, (E) bone recurrence, and (F) lung recurrence as first event according to histologic type.

and the remaining 9% were various rarer entities, such as mucinous, tubular, medullary, comedo, papillary, and other histologic types.[1] Our analysis includes 12,206 patients with known histology treated on 15 adjuvant IBCSG trials accruing from 1978 through the year 2002 with excellent prospective collection of clinical and pathologic data.[9-20] Similar proportions of histologies were found.

Largely in agreement with other series, we found significant although quantitatively small differences in baseline patient and tumor

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Table 4. Site-Specific Cumulative Incidence of Local Recurrence, Contralateral Breast Cancer, Regional Recurrence, Distant Recurrence, Bone Metastases, and Lung Metastases According to Histologic Type in All Patients, Within the ER-Negative Cohort, and Within the ER-Positive Cohort

	Cumulative Incidence										
	Infiltrating Ductal					Infiltrating Lobular					
Site	5 Years	10 Years	15 Years	20 Years	25 Years	5 Years	10 Years	15 Years	20 Years	25 Years	*P*
All patients											
Local	8.3	10.4	11.4	11.9	11.9	6.7	10.4	12.3	13.3	13.3	.94
Contralateral	1.9	3.4	4.7	5.7	6.3	2.6	4.6	6.4	8.1	8.1	.07
Regional	7.1	8.7	9.1	9.4	9.8	2.2	4.2	4.9	4.9	4.9	< .01
Any distant	20.7	26.5	29.1	30.7	31.8	18.7	29.5	33.4	37.0	37.0	.13
Bone	10.7	14.0	15.5	16.2	16.7	12.6	19.2	21.0	22.7	22.7	< .01
Lung	5.5	6.9	7.5	7.9	8.2	1.0	1.5	2.0	2.0	2.0	< .01
ER negative											
Local	9.1	10.2	10.6	10.9	10.9	9.8	13.9	13.9	13.9	—	.26
Contralateral	1.6	3.4	4.1	5.2	5.7	3.0	4.8	8.5	11.8	—	.10
Regional	10.2	11.3	11.6	11.8	12.1	4.8	4.5	4.5	4.5	—	.01
Any distant	25.4	29.3	30.7	31.2	34.2	18.8	31.8	37.2	39.6	—	.73
Bone	10.5	12.3	13.0	13.2	13.4	14.3	20.7	22.2	24.6	—	< .01
Lung	7.6	8.6	8.8	8.8	9.8	1.5	2.5	2.5	2.5	—	< .01
ER positive											
Local	7.7	10.3	11.9	12.7	12.7	6.2	9.5	12.1	13.8	—	.72
Contralateral	1.9	3.5	5.1	6.2	6.7	2.7	5.0	6.4	7.3	—	.22
Regional	5.0	6.8	7.4	7.7	8.4	1.9	3.8	4.7	4.7	—	< .01
Any distant	17.8	24.4	27.8	30.2	31.3	18.7	28.7	32.4	36.7	—	.04
Bone	10.3	14.3	16.4	17.5	18.6	12.0	18.6	20.5	21.9	—	.02
Lung	4.5	6.0	7.0	7.8	7.8	1.0	1.5	1.8	1.8	—	< .01

Abbreviation: ER, estrogen receptor.

characteristics between ILC and IDC patients. Patients with ILC were older.[2,5,6] Tumor size was slightly increased in ILC,[2,5] whereas axillary nodal involvement was comparable.[5] As expected, ER status in ILC was more often positive.[2,4-6,28] Vessel invasion was seen less often in ILC compared with IDC. Our finding of only 11.7% of ILC with tumor grade 3 compared with 41.7% of IDC is consistent with other reports.[2,6,28] In addition, the higher incidence (11.2%) of unknown grade in ILC compared with IDC (1.5%) is probably a result of pathologists' decisions not to grade some ILC, whereas almost all IDC were gradable. Indeed, tumor grading is based on three features involving semiquantitative evaluation of percentage of tubule formation, degree of nuclear pleomorphism, and mitotic count using a defined field area.[29] Pathologists have been reluctant to use this grading system for ILC primarily because of the absence of any tubule formation in ILC, rendering that dimension of the three-tiered grading system redundant.

Some surprising features of the study population were observed, specifically the higher than expected frequency of lobular tumors that were also ER negative or had vessel invasion. Although we cannot find an explanation for these findings, we were reassured that the results were the same if we excluded these patients from the lobular population.

Our finding that ILC was treated less often with breast-conserving surgery than IDC was consistent with others' findings.[3-6] This is regularly attributed to the increased difficulty in defining tumor margins clinically, radiologically, and histologically in ILC. In one series, the rate of conversion from breast-conserving surgery to mastectomy was increased in ILC.[3] However, there is recent evidence that breast-conserving surgery in ILC is not associated with increased local relapse rates at 5 years when compared with mastectomy.[3,8] Although there are no randomized data specifically comparing breast-conserving surgery with mastectomy in ILC, most would agree that ILC can and should be treated with breast-conserving surgery (and radiotherapy) when clear margins can be achieved.[5,8]

Although the choice of surgery is related to the clinician's judgment, it may also influence local relapse rates. Of seven studies reporting on 5-year local relapse rates comparing ILC versus IDC, five studies found increased local relapse rates for ILC, whereas two found the opposite.[8] We did not find an increase in local relapse rates for ILC compared with IDC.

Compared with IDC, ILC is known to be more often multifocal, multicentric, and bilateral.[5] In a large retrospective series, ILC was found to be associated with an increased risk of contralateral breast cancer (20.9% in ILC *v* 11.2% in IDC; median follow-up time, 87 months).[5] In our prospective series with a median follow-up time of 13 years, contralateral breast cancer was infrequent in ILC (8.1% at 20 years), and the difference compared with IDC (5.7% at 20 years) was not significant. Similarly, there was no difference in the frequency of axillary lymph node metastases in our study as well as in many other studies.[2,3,5] In our series, regional relapse was less frequent in ILC compared with IDC. To our knowledge, this finding has not been previously described.

The inconsistent findings of others regarding prognosis[2,5,6] might be reconciled by the interesting observation made in our series with a long follow-up. Although prognosis was better for ILC compared with IDC during the first years of follow-up, it became worse for ILC during later years starting at approximately 6 years after diagnosis. It is interesting to note that similar observations have been made

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comparing ER-positive breast cancer with ER-negative breast cancer.[30,31] Although recurrence rates in ER-positive breast cancer are less than in ER-negative breast cancer during initial years, recurrence rates in later years are reversed. Because ILC is more likely to be ER positive than IDC, these similar observations for ER-positive carcinoma and for ILC are plausible and could be, at least in part, related. Surprisingly, the curves have similar shape for the ER-negative and ER-positive subgroups, indicating that ILC is associated with a significantly better early prognosis and a significant worse late prognosis independent of ER status. It is possible that the absence of anthracycline-containing chemotherapy in the earlier studies contributed in part to the worse outcome for ILC later in follow-up.

Concerning the pattern of metastatic spread, ILC has a less stereotyped pattern than IDC, more frequently involving unusual sites such as the GI tract and the meninges.[32] We found a decreased frequency in lung metastases in ILC, in agreement with others.[5] An unexpected finding was the higher frequency of bone metastases in ILC, which was a significant difference that increased with time. To our knowledge, this finding has not been previously described. Although these differences are not large, they are interesting to note and likely related to the biology and the genetic makeup of these tumors.[33] They might be somehow related to the loss of the adhesion molecule E-cadherin in ILC cancer cells as a result of the loss of the *CDH1* gene on chromosome 16q22.1. Although it is generally accepted that the loss of E-cadherin and of adhesion function is related to the dispersed histology of ILC, it is more difficult to explain an increase of bone metastases and a decrease of lung metastases and regional metastases by such changes. It is likely that factors governing metastatic potential and tropism for particular organs are many and complex, involving not only tumor cells, but stromal, endothelial, and other cells as well as extracellular matrix and signaling molecules. Our study should be an incentive for basic research to further uncover such mechanisms.

This large study with prospective data collection and relatively long follow-up helps clarify the differences between IDC and the less common ILC. ILC occurs in older patients, and tumors tend to be larger, well or moderately well differentiated, and ER positive and only rarely show vessel invasion. ILC is more often treated with mastectomy than IDC probably because of uncertainty about its margins. Prognosis for ILC tends to be better than for IDC in early years, but relapse tends to become progressively more frequent and surpasses IDC at approximately 6 years. This time-dependent effect was largely independent of ER status. Local relapse and contralateral breast cancer were not significantly increased in ILC. Future bone metastases are more frequent with ILC, whereas regional and lung metastases are less frequent. We are hopeful that the portrait carved of ILC will be helpful to the clinician and the researcher alike in our efforts to dissect the clinical and biologic heterogeneity of invasive breast cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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