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Tumor Biology of Infiltrating Lobular Carcinoma

Implications for Management

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Objective
The purpose of this study was to characterize the biologic determinants that affect the behavior and management of infiltrating lobular cancer.

Methods
A prospectively accrued data base containing 1548 breast cancer cases was queried for specific pathologic and mammographic features. From this data base, 777 patients treated and followed-up at the H. Lee Moffitt Cancer Center were reviewed, and comparisons were made between the following three histologic subgroups: 661 infiltrating ductal (ID), 42 infiltrating ductal plus infiltrating lobular (ID + IL), and 74 infiltrating lobular (IL).

Results
Comparisons of the three histologic forms of breast cancer demonstrated the following:

1. At diagnosis, tumors with IL components were larger than those with ID components ($p < 0.001$); in addition, a greater percentage of IL cancers were T3 lesions (14.8%), compared with ID cancers (4.5%).
2. Sizes of IL tumors were underestimated frequently by mammographic examinations when compared with pathologic measurements ($p < 0.001$).
3. By comparison to ID tumors, increasing IL tumor size is less likely to be associated with an increased number of metastatic lymph nodes per patient ($p = 0.09$).
4. Infiltrating lobular cancers treated by lumpectomy with cytologic surgical margin analysis more often gave false-negative results than did ID cancers ($p < 0.001$).
5. Infiltrating lobular cancers treated by lumpectomy required conversion to mastectomy over 2 times more frequently than ID cancers treated by lumpectomy.
6. Mastectomy was performed more frequently than lumpectomy for the treatment of IL *versus* ID tumors ($p = 0.039$).

Conclusions
Infiltrating lobular cancers are biologically distinct from ID cancers. Although lumpectomy may be performed safely in selected patients, multiple difficulties exist in the management of IL cancer, particularly when breast conservation is chosen.

Invasive lobular (IL) carcinoma is an insidious variant of breast cancer. Its presentation may be subtle and its extent often underestimated. Infiltrating lobular cancers may be multicentric and often invade beyond regions of suspicion, as evidenced by clinical findings.[1,2] In addition, IL lesions may be difficult to detect mammographically.[3] Despite these observations, recent reports of low recurrence rates with conservative surgical approaches have been made, suggesting that many IL tumors may be appropriately treated by lumpectomy and radiotherapy.[4–7]

Numerous cases in which preoperative mammogram results were thought to be normal yet by final pathologic review were found to involve tumor (Fig. 1A & B) stimulated us to review all of the cases of IL cancer recorded in the prospective breast cancer data base at the H. Lee Moffitt Cancer Center. We hypothesized that IL cancers are biologically distinct from infiltrating ductal (ID) cancers. To test this hypothesis, we reviewed a study group composed of patients with breast cancer representing three different histologic subtypes. Infiltrating lobular cancer cases were compared with infiltrating ductal and mixed cases, where ID and IL histologic findings were present. Comparisons were made regarding pathologic and mammographic tumor size, TNM stage, lymph node status, estrogen receptor/progesterone receptor (ER/PR), type of surgical procedure, and survival analysis.

MATERIAL AND METHODS

Clinical data from 1548 breast cancer patients treated at the H. Lee Moffitt Cancer Center and Research Institute at the University of South Florida, Tampa, were accrued prospectively over the course of 9 years in a computerized data base and an independent cancer registry. Data elements recorded in the prospective, computerized, relational data base included 425 different variables. From this data base, information on 917 patients treated and followed up at the H. Lee Moffitt Cancer Center for whom complete data were available was abstracted according to specific pathologic and mammographic features (Table 1). Comparisons were then made between 777 patients (the study population) divided into three separate histologic subgroups: 661 ID cancers, 74 IL cancers, and 42 mixed ID-plus-IL cancers. To be included among one of these subgroups, patients were required to have a single (unilateral) invasive breast cancer (ID, ID + IL, or IL); however, some patients included in each group had more than one tumor histologic feature (i.e., ID/ductal carcinoma *in situ* [DCIS] or IL/lobular carcinoma *in situ*). We confirmed the data derived from the data base by cross-checking with data collected by the H. Lee Moffitt Cancer Center cancer registry. The number of patients identified by the cancer registry in each of the three study subgroups was identical to that derived from the prospective data base. This registry collects fewer variables but reports a 98% follow-up record, because the patients are contacted yearly by mail.

Comparative analyses of multiple variables included pathologic and mammographic tumor size, tumor stage at diagnosis, lymph node status, ER/PR levels, type of surgical procedure, assessment of lumpectomy surgical margins by touch-preparation analysis, and survival. Statistical analyses of all data were performed and estimates of significance made. Not all information (e.g., mammographic tumor size) was available on all patients; consequently, numbers of patients in particular portions of this analysis were fewer than in the entire study population.

A representative subset of IL cancers was analyzed and mammographic tumor size calculated. Final pathologic tumor size was compared with these blinded mammographic tumor measurements. An experienced mammographer (M.M.) reread multiple cases of known IL cancer and measured mammographic tumor size in two dimensions. The larger of the two measured dimensions was then compared with pathologic measurements.

Statistical analysis was performed independently by one of the authors (A.C.) by means of the SAS statistical software package (SAS Institute, Inc., Cary, NC). Analyses included contingence table chi square, paired t test, pooled t test, analysis of variance, log-rank test, and Fisher's z transformation for correlation coefficients. Probability values (all-sided) are listed in each table and figure where appropriate.

RESULTS

Composition of Study Population

A total of 1548 cancer cases were reviewed for the purpose of this study. From this group, we selected 917 patients with unilateral breast cancers of variable histologic type (Table 1) who were treated surgically and followed up at the H. Lee Moffitt Cancer Center. From these 917 patients, 777 were selected by histologic type as the study population (Table 2). The study population comprised three subgroups: 661 ID patients (85%), 75 IL patients (10%), and 42 patients (5%) with mixed ID-plus-IL histologic types in the same breast. The study group represented a smaller number of patients than the total number available because only patients for whom adequate

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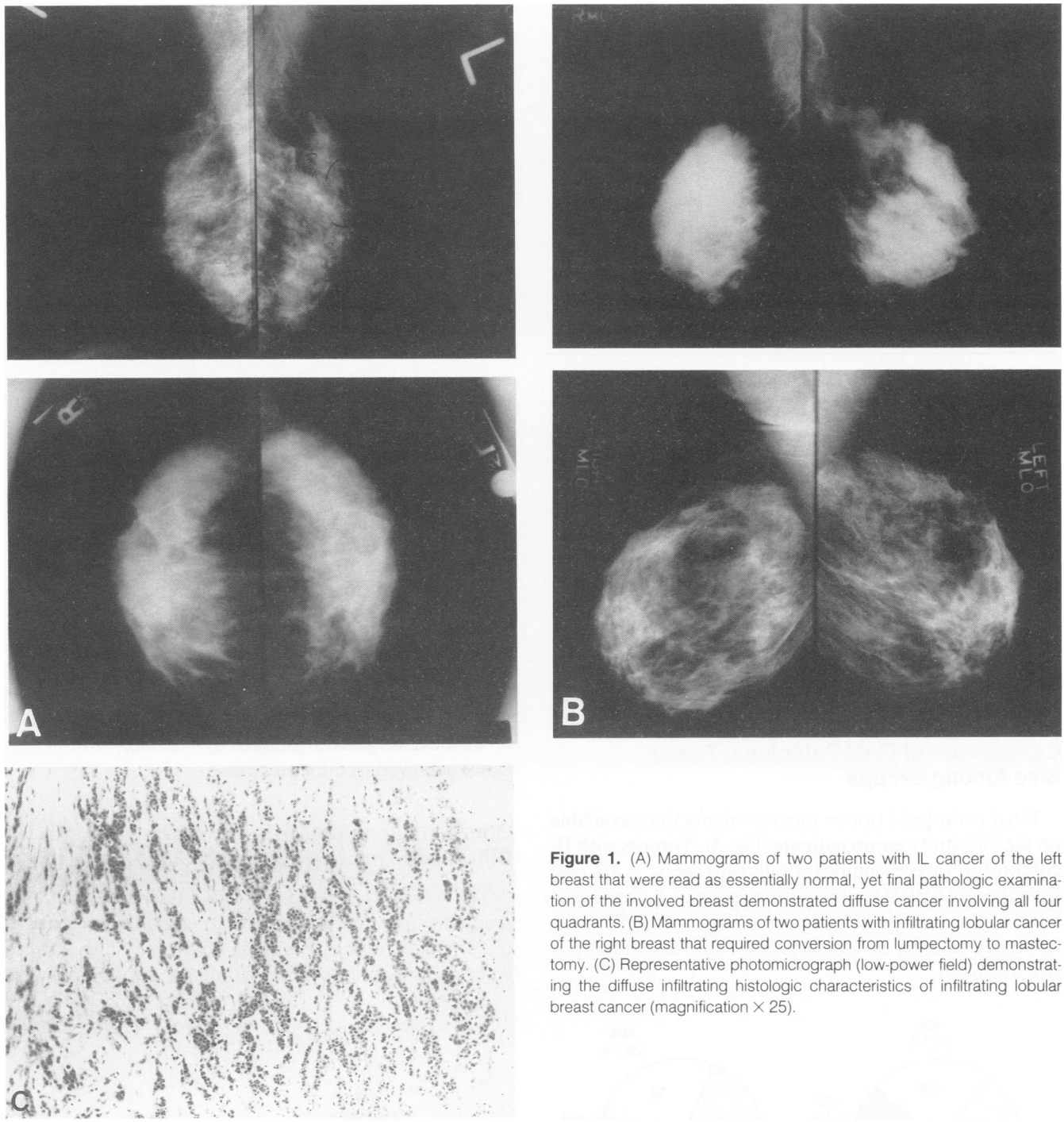

Figure 1. (A) Mammograms of two patients with IL cancer of the left breast that were read as essentially normal, yet final pathologic examination of the involved breast demonstrated diffuse cancer involving all four quadrants. (B) Mammograms of two patients with infiltrating lobular cancer of the right breast that required conversion from lumpectomy to mastectomy. (C) Representative photomicrograph (low-power field) demonstrating the diffuse infiltrating histologic characteristics of infiltrating lobular breast cancer (magnification × 25).

evaluable data were available (in the three histologic subgroups) as well as patients who were initially treated and followed up on site were included.

Because the natural history of breast cancer demonstrates a protracted time to recurrence, median follow-up times were examined to determine if adequate time had passed for accurate assessment of survival for various subpopulations of patients. Median follow-up was defined as the time for which 50% of the study population had been observed. Median follow-up was shortest for the IL group (3.08 years) and longest for the ID group (3.39 years) (Table 2).

Analysis of Age at Presentation: All Subgroups

The age distribution at presentation of each histologic subgroup was essentially the same, the exception being

Table 1. BREAST CANCER PATIENTS TREATED AND FOLLOWED UP AT THE H. LEE MOFFITT CANCER CENTER

Tumor Histology	Incidence	%
ID	661/917	72.1
IL	74/917	8.1
ID + IL	42/917	4.6
DCIS	95/917	10.4
LCIS	6/917	0.7
Other	38/917	4.1

ID = infiltrating ductal; IL = infiltrating lobular; DCIS = ductal carcinoma *in situ;* LCIS = lobular carcinoma *in situ.*

Table 2. MEDIAN FOLLOW-UP FOR BREAST CANCER PATIENTS IN STUDY POPULATION

Tumor Histology	n	%	Median Follow-up (days/years)
ID	661	85.1	1254/3.43
ID + IL	42	5.4	1233/3.37
IL	74	9.5	1144/3.13
Total	777		

ID = infiltrating ductal; IL = infiltrating lobular.

the percentage of patients younger than age 39 in the IL group, which was 5.4% *versus* 11.8% and 11.9% in the ID and ID-plus-IL groups, respectively (Fig. 2).

In a separate correlation analysis, age and tumor size were compared for each subgroup (ID, ID + IL, and IL). Only ID tumors demonstrated a significant, negative correlation ($r = -0.149$, $p = 0.0003$), suggesting that older patients tend to present with smaller tumors. Despite the r value being relatively small, the correlation was highly significant and unlikely due to chance because of the large sample size (n = 671).

Comparison of Final Pathologic Tumor Size Among Groups

Final pathologic tumor measurements were available on the 785 study group patients (Fig. 3). Tumors with IL composition were significantly larger (mean = 3.2 cm) than tumors with ID composition (mean = 2.2 cm) ($p < 0.001$). The tumors of mixed histologic type (ID + IL) fell in between the ID and IL groups, with a mean tumor size of 2.6 cm.

Initial Comparison of Pathologic and Mammographic Tumor Size: Infiltrating Lobular Subset

In an initial study, data on 39 IL patients for whom original mammograms of sufficient quality were available were subjected to blinded review by an expert mammographer (M.M.). The mean mammographic tumor sizes of these cancers were compared with the mean pathologic sizes for these tumors. The mean pathologic tumor sizes were larger than mean mammographic sizes by more than 12 mm ($p = 0.016$, paired two-tailed t test) (Table 3). In the study, mammograms results read as normal were assigned a tumor size of 0.0 mm ($p = 0.016$) or were excluded from analysis ($p = 0.036$), with significance achieved by either method.

Comparison of Mean Tumor Size Differences Among the Three Subsets

The positive results of our initial review led us to examine the measured differences in pathologic and mammographic tumor size among the three study groups when mammographic and pathologic tumor sizes were

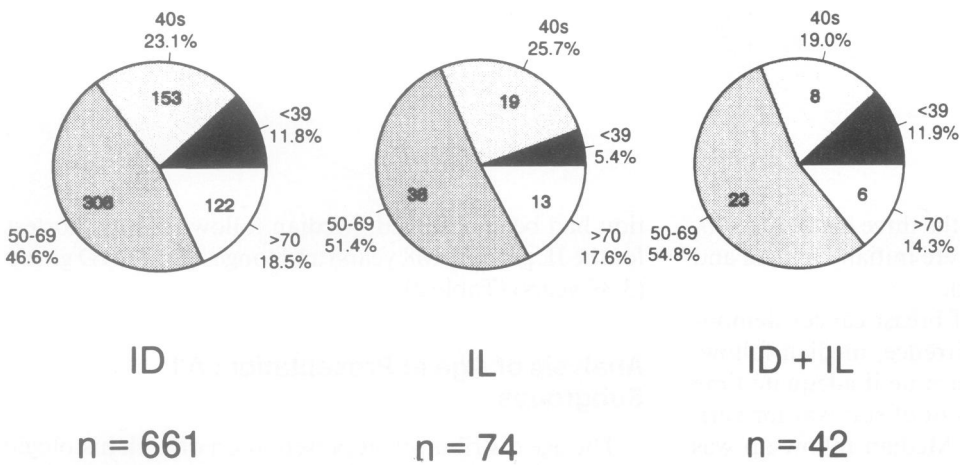

Figure 2. Age distribution of all patients entered in the breast cancer data base. All distributions were similar with the exception of the IL group, in which only 5.4% of patients were younger than age 39 at presentation.

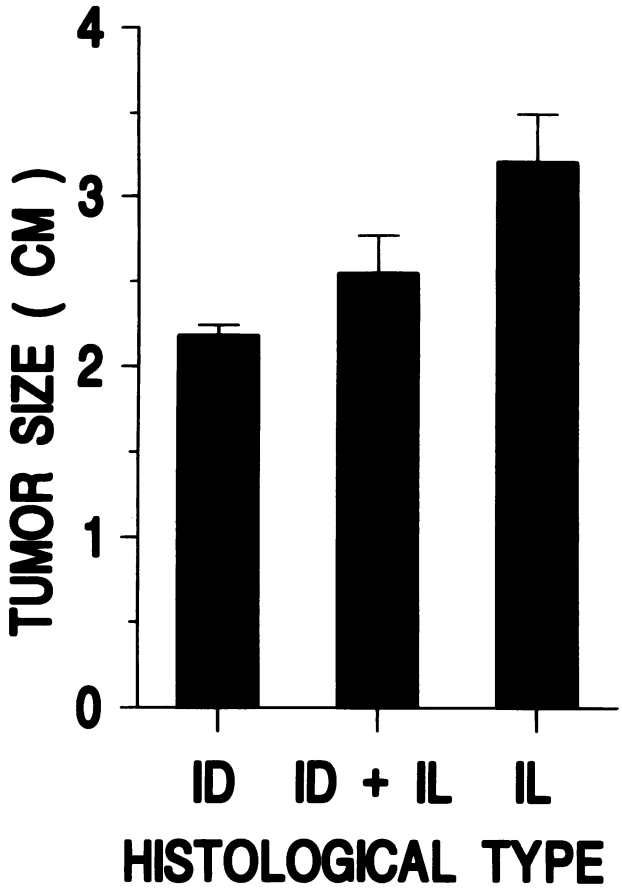

Figure 3. Mean tumor size derived from final pathologic reports was plotted for each tumor subgroup. Infiltrating lobular tumor sizes were found to be significantly larger than ID tumor sizes ($p < 0.001$, one-way analysis of variance).

available through the computerized data base. For each case within each group, the difference between pathologic tumor size and mammographic tumor size was calculated in millimeters. Data were reported as the means of the differences in millimeters for each histologic group (Table 4). These results not only confirmed our initial review data, which suggested that mammograms undersized IL cancers by more than 10 mm ($p < 0.0001$), but also suggested that all three subgroups of tumors were significantly undersized by mammography, with difference being greater among IL cancers compared with ID and ID-plus-IL cancers. Although the mean difference between pathologic and mammographic tumor size was greater for the IL group (10.2 mm) than for the ID group (5.2 mm), the comparison of these differences did not reach statistical significance ($p = 0.08$).

Table 3. SELECTED SECONDARY REVIEW OF INFILTRATING LOBULAR CANCERS: PATHOLOGIC VERSUS MAMMOGRAPHIC TUMOR SIZE

Parameter	Tumor Size (mean ± SD) (mm)*
Mammographic	19.9 ± 13.9
Pathologic	32.1 ± 30.5

* n = 39, p = 0.0157, paired t test. When mammographic tumor measurements of 0.0 mm were excluded from analysis (3 patients), p = 0.0363.

Table 4. A COMPARISON OF MEANS FOR DIFFERENCES BETWEEN PATHOLOGIC AND MAMMOGRAPHIC TUMOR SIZES

Tumor Histology	n*	Mean Tumor Size (Δ(pathologic − mammographic)(mm)]	p Value†
ID	297	5.2	<0.0001
ID + IL	21	6.9	0.0216
IL	38	10.6	0.0016

ID = infiltrating ductal; IL = infiltrating lobular.
* Mammographic data were not available on all patients in the study population.
† p values derived using paired t test. p = 0.08 for a comparison of ID differences vs. IL differences, pooled t test.

Analysis of Lymph Node Involvement With Metastatic Disease

Pathologic staging of lymph node involvement for the study group was accomplished by recording the number of positive lymph nodes per total lymph nodes sampled. The incidence of patients with positive lymph nodes in each subgroup of patients was determined, as was the mean number of positive nodes per case (in cases in which at least one positive lymph node was detected) (Table 5). The IL subgroup had a higher incidence of nodal positivity (51%) compared with the ID-plus-IL (43%) and ID (36%) subgroups (p = 0.025). No signifi-

Table 5. INCIDENCE OF POSITIVE LYMPH NODES

Tumor Histology	Incidence	% Positive	Positive LN/Patient (mean ± SD)*
ID	237/661	36	5.1 ± 6.6
ID + IL	18/42	43	3.1 ± 3.3
IL	38/74	51	6.6 ± 9.0
p value		0.025†	NS‡

LN = lymph node; ID = infiltrating ductal; IL = infiltrating lobular; NS = not significant.
* Only patients with at least one positive node were included in this analysis.
† Chi square.
‡ ANOVA.

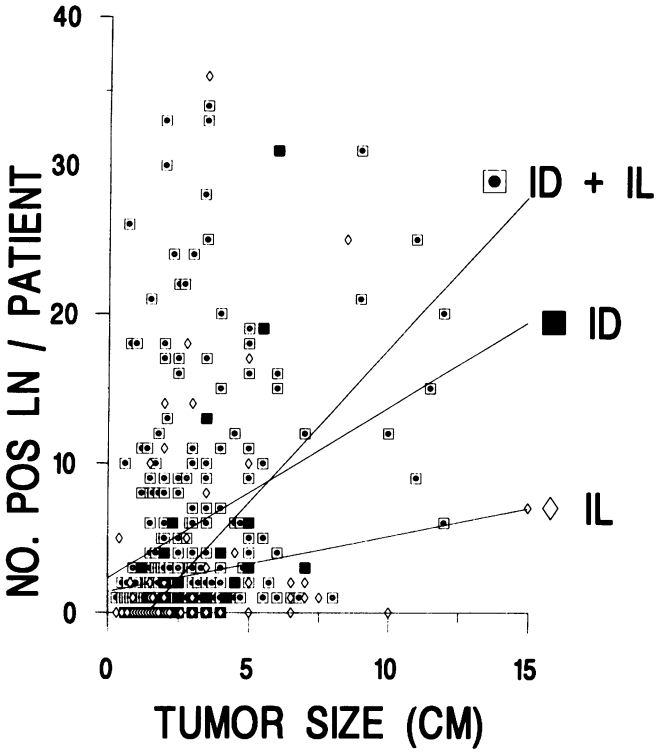

Figure 4. Linear regression analysis of pathologic tumor size *versus* number of positive lymph nodes per patient for three tumor histologic types. Infiltrating lobular tumors were significantly different than ID-plus-IL tumors ($p = 0.02$) and marginally different than ID tumors ($p = 0.09$) (Fisher's z test). These data suggest that IL tumors, unlike ID and ID-plus-IL tumors, are less likely to produce more positive nodes as they grow.

cant differences in the mean number of positive nodes were found among the patients diagnosed with at least one positive node.

Analysis of Pathologic Tumor Size *Versus* Number of Positive Lymph Nodes per Patient

To better understand the biologic features of IL cancer, we used a scattergram to plot pathologic tumor size against number of positive lymph nodes per patient (Fig. 4). We then analyzed linear regression and found that the correlation coefficients for each regression line differed. Using the Fisher's z transformation, we found that correlations for IL tumors differed significantly from those found for ID-plus-IL tumors ($p = 0.02$) and differed marginally from those found for ID tumors ($p = 0.09$). Infiltrating lobular tumor sizes tended to correlate less with the number of positive nodes than did ID and ID-plus-IL tumors. Similar comparisons were performed between tumor size and ER/PR levels recorded for each tumor but were not significantly different.

Stage at Diagnosis

The TNM stage at diagnosis for the three study subpopulations was examined to determine any staging

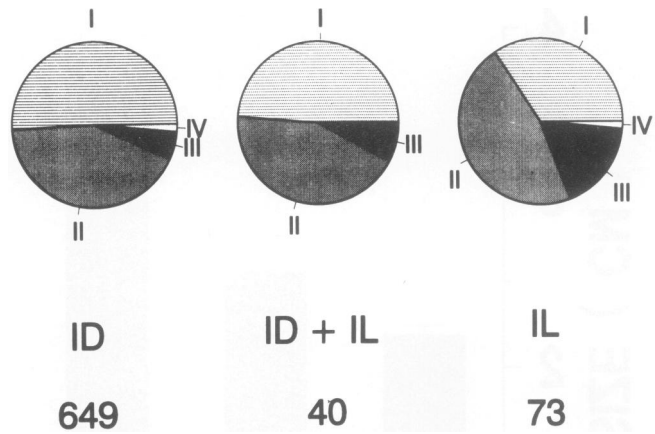

Figure 5. Stage at presentation was determined for the majority of patients in the three study subgroups. Infiltrating lobular tumors included more stage III and fewer stage I patients on a percentage basis.

differences between histologic subtypes. The most pertinent observation was that IL patients presented with fewer tumors in stage I and more tumors in stage III compared with the ID and ID-plus-IL groups. These data suggest that more IL tumors are T3 (large) lesions (Fig. 5) at the time of diagnosis. A subsequent analysis revealed that 4.5% of ID lesions *versus* 14.8% of IL lesions were T3 lesions at diagnosis.

Analysis of Estrogen and Progesterone Receptor Levels Among Subgroups

Levels of ER and PR were recorded for the majority of patients in each subgroup of the study population. Patients with ER or PR values greater than 10 fmol/mg were considered to have positive receptors. The inci-

Table 6. ER/PR LEVELS VERSUS TUMOR HISTOLOGY

Tumor Histology	n	+ER (%)*	ER Level (mean ± SD)
ID	454	72.0	168 ± 184
ID + IL	32	78.1	174 ± 181
IL	50	88.0†	110 ± 139
		+PR (%)*	
ID	428	66.8	265 ± 288
ID + IL	31	64.5	271 ± 248
IL	50	68.0	246 ± 241

ER = estrogen receptor; PR = progesterone receptor; ID = infiltrating ductal; IL = infiltrating lobular; NS = not significant.

* ER/PR levels were considered positive if > 10 fmol/mg.

† $p = 0.015$ for a comparison of ER levels for ID *vs.* IL, chi square; p = NS for all other comparisons.

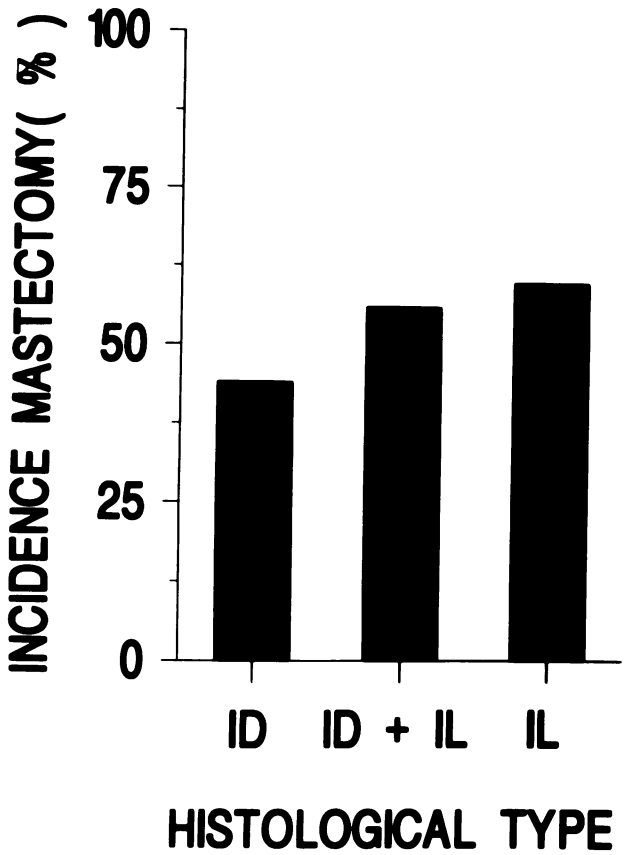

Figure 6. Incidence of mastectomy *versus* histologic tumor type. Approximately 60% of patients in the IL group underwent mastectomy *versus* 44% in the ID group (p = 0.039, chi square).

dence of ER positivity was calculated to be greatest for the IL group (88% ER positive), which differed significantly from the ID group (72% ER positive) (p = 0.015) (Table 6A). No differences between histologic subgroups regarding the number of patients with positive PR levels were recorded (Table 6B). The degree of positivity among those patients with positive ER or PR levels was then estimated by means of a mean value for each subgroup. Again, no significant differences were noted.

Analysis of Type of Surgical Procedure Among Subgroups

All three study subgroups were examined for the incidence of lumpectomy plus axillary lymph node dissection *versus* mastectomy, and significantly more IL patients (60%) were found to have undergone mastectomy compared with ID patients (44%) (p = 0.039) (Fig. 6). Procedural (surgical) differences between these subgroups and the ID-plus-IL subgroup were not significant.

This higher rate of mastectomy for the IL group was distinctly different from the rate of mastectomy for the ID group as well as from the overall rate of mastectomy for all patients treated at the H. Lee Moffitt Cancer Center. Data retrieved from the cancer registry documented an overall rate of mastectomy of 45.5% for 1047 patients of all histologic types, with the remainder of the patients (54.5%) treated with breast conservation. The mastectomy rate for the ID cancers was 44%.

Analysis of Patients Among All Subgroups Requiring Immediate Conversion From Lumpectomy to Mastectomy

All cases in which mastectomy was performed were analyzed for the occurrence of an ipsilateral lumpectomy within 1 month of mastectomy. Cases in which initial attempts at planned lumpectomy failed secondary to positive intraoperative margins (even after 3–4 attempts at obtaining new, tumor-free margins were made) were enumerated (Table 7). Cases in which salvage mastectomy was performed for recurrent disease were excluded from this analysis. A statistically significant difference was found, with approximately 2.5-fold more patients requiring conversion from lumpectomy to mastectomy in the IL group (17.5%) than in the ID group (6.9%) (p = 0.018). Data regarding the DCIS group also revealed frequent conversion (9.3%) from lumpectomy to mastectomy.

Analysis of Intraoperative Touch-Preparation Margins During Lumpectomy

Touch preparations of resected lumpectomy specimens are performed routinely at the H. Lee Moffitt Cancer Center and Research Institute in preference to frozen section in order to improve sensitivity and reduce intraoperative pathologic assessment times.[8] Analysis of

Table 7. CONVERSION RATES FOR LUMPECTOMY TO MASTECTOMY

Tumor Histology	Incidence*	%†	Mean Age (yr)
ID	28/405	6.9	48.4
ID (pure)	10/251	4.0	
ID/DCIS	17/152	11.2	
ID/LCIS	1/2	50.0	
IL	7/40	17.5	55.1
IL (pure)	4/28	14.3	
IL/LCIS	2/10	20.0	
IL-DCIS	1/2	50.0	
DCIS (pure)	8/86	9.3	55.0

ID = infiltrating ductal; IL = infiltrating lobular; DCIS = ductal carcinoma *in situ*; LCIS = lobular carcinoma *in situ*.

* Denominator represents no. of patients converted (from lumpectomy to mastectomy) + total no. of lumpectomy patients.

† p = 0.058 for all groups; p = 0.018 for ID *vs.* IL, chi square.

Table 8. INTRAOPERATIVE MARGIN ANALYSIS: SENSITIVITY OF TOUCH PREPARATIONS

	IL (n = 35) (%)	ID (n = 289) (%)	p Value*
False-negative	11.0	1.0	<0.001
False-positive	6.0	3.0	NS

IL = infiltrating lobular; ID = infiltrating ductal; NS = not significant.
* Chi square.

touch-preparation margins demonstrated a higher percentage of false-negative results for patients with IL cancers (11%) *versus* those with ID cancers (1%) ($p < 0.001$). Although false-positive rates were higher for IL than for ID cancers, these differences were not statistically significant (Table 8).

Survival and Disease-Free Survival

No significant differences were found between disease-free survival and survival among the three histologic subgroups (Fig. 7). Similarly, no significant differences in survival were found between groups analyzed by TNM stage. Median follow-up times for each study subgroup are listed in Table 2.

DISCUSSION

Infiltrating lobular cancer is an unusual form of invasive breast cancer that has distinctive pathologic characteristics. First described by Cornil[9] in 1865, IL tumor is diffusely infiltrative and is composed of small, round, regular cells that form single lines throughout a desmoplastic stroma (Fig. 8). Infiltrating lobular tumors range in size from small, microscopic lesions to diffusely infiltrating carcinomas involving the entire breast. The latter form may occasionally mimic inflammatory carcinoma.

The biologic behavior of IL cancers has been reported to be unique, regarding not only the pattern of primary tumor growth, but also the pattern of metastatic spread.[10] For example, IL cancer has been associated with meningeal carcinomatosis more frequently than have other histologic types of breast cancer that tend to produce nodular, organ-specific parenchymal, metastatic foci. In addition, in some series, the incidence of bilateral breast cancer has been reported to be as high as 30%, twice the rate reported for other forms of invasive breast carcinoma.

Within the context of a multidisciplinary breast care conference, some of the distinctive characteristics of IL cancer became apparent. In our comprehensive breast care center, all patients undergoing treatment were represented in a conference during which pathologic slides and mammograms were reviewed as well as surgical and pathologic end results. We evaluated multiple cases in which mammogram results were normal or which identified small tumors, yet final pathologic examinations documented the presence of significantly larger tumors—some diffuse throughout the breast (Fig. 1 A and B). These cases involving insidious disease led us to hypothesize that many of the difficulties experienced before and during surgery are related to the unique biologic features and diffuse growth patterns of IL cancers. To identify the biologic determinants that affect the behavior and management of IL cancer, we evaluated a large computerized data base. A study population was selected from the data base for whom multiple biologic and clinical parameters were available. Three histologically distinct subpopulations were assessed for age, stage at diagnosis, and incidence of positive lymph nodes.

Although it has been reported that the greatest percentage of IL cancers occur among women older than age of 70,[11] we could not reproduce this finding. Our population of IL patients was similar in age distribution to patients with ID or ID-plus-IL cancers, most of whom were younger than age 70 (Fig. 2). In analyzing age distributions, we observed that fewer IL patients were younger than age 39 compared with the other groups. In addition, we found that older patients in the ID group had smaller tumors ($p = 0.0003$), a finding not associated with the IL cancers, which are known for their diffuse, infiltrating nature.

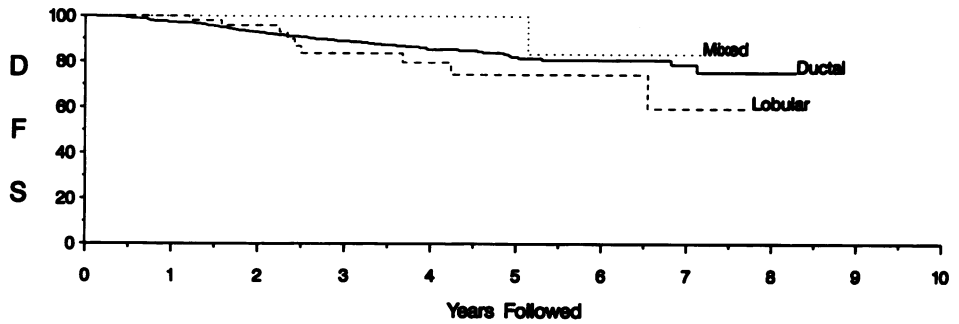

Figure 7. Overall Kaplan–Meier survival curves for the three study groups. No significant differences were detected (log-rank test).

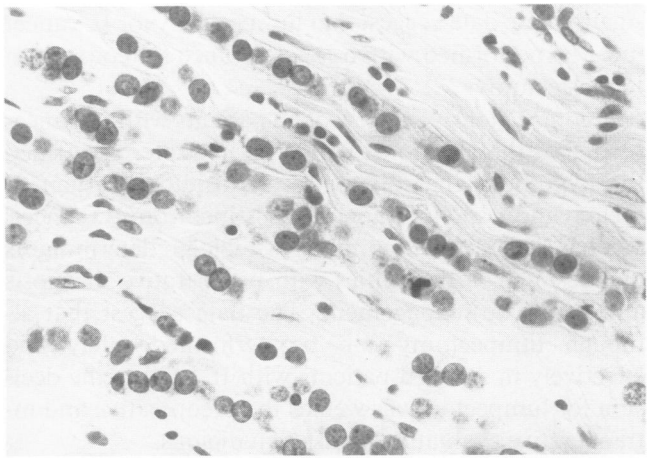

Figure 8. High-power photomicrograph of a typical IL cancer, in which tumor cells form single lines among a dense desmoplastic stroma (magnification × 500).

Because of the clinical observation that IL tumors tended to be palpably large and mammographically undetectable (either unrecognized or underrecognized), we examined the pathologic tumor sizes of each of our study subpopulations. The data suggested that significant differences in tumor size existed between ID and IL subgroups, with the ID-plus-IL group falling in between (Fig. 3). These data led us to review mammographic tumor size *versus* pathologic tumor size. This review initially included only IL patients treated at the H. Lee Moffitt Cancer Center for whom original preoperative mammograms were available and re-readable, in a blinded fashion, by an expert mammographer (M.M.). Among the 39 evaluable patients, mean pathologic tumor sizes exceeded mean mammographic tumor sizes by more than 10 mm at a significant level ($p = 0.0157$). Because this initial evaluation included three patients whose mammogram results were confirmed to be without evidence of cancer (scored as 0.0 mm), we reevaluated the data without these patients and still found significant differences.

Further in-depth study of recorded mammographic and pathologic tumor size demonstrated similar findings to our initial review. These data confirmed that mean IL pathologic tumor sizes were approximately 10-mm larger than mean mammographic tumor sizes ($p = 0.0016$). In addition, they demonstrated that mammographic evaluations can underestimate or miss IL cancer and that similar yet less obvious differences are present in other tumors. Likewise, the literature suggests that IL cancers are often difficult to detect mammographically.[3,12,13] Although the majority of IL cancers exhibit spiculated opacity, they can also appear as a poorly defined architectural distortion. The low level of opacity and poor margination of these tumors have been attributed to their tendency to grow diffusely in multicentric foci with intervening, desmoplastic tissue. Despite the proclivity for mammography to underestimate the size of any tumor, we have found that mammographic tumor sizes closely correlated with pathologic tumor sizes ($r = 0.74$) when all infiltrating tumors were grouped together.[14]

A linear regression analysis of number of positive lymph nodes per patient *versus* tumor size suggested that IL tumors, unlike ID or ID-plus-IL histologic types, do not necessarily metastasize with a higher frequency as tumor size increases (Fig. 4). Analysis of stage at diagnosis revealed more stage III patients and more T3 cancers in the IL group (Fig. 5), yet overall survival for IL patients was no different than for ID patients (Fig. 7). Taken together, these findings have led us to postulate that IL tumors are biologically different from ID tumors. Subsequently, an analysis of the number of patients with metastatic lymph nodes in each histologic group revealed that more IL cancer patients had positive nodes (Table 5), although there were no differences in the mean number of positive nodes per patients among patients known to have at least one positive node. On explanation for the apparent dichotomy of more positive nodes in the IL group yet fewer positive nodes associated with increasing tumor size is that IL cancers metastasize earlier but are less likely to metastasize as tumors grow larger, as compared with ID tumors. In fact, the median number of positive nodes in the stage III patients for the IL group was two, whereas for the the ID group it was 4.5.

Because IL tumors have been reported to have higher rates of ER positivity, we evaluated all three study groups for this parameter as well as for PR positivity and found a significant trend toward more IL tumors than ID tumors being ER positive (see Table 6) ($p = 0.015$). We found no difference between groups regarding the number of PR-positive tumors, nor did we find any differences between groups for mean ER and PR levels in femtomoles per milligram among patients with positive levels.

Analysis of the type of surgical procedure selected for each patient subgroup demonstrated findings that were empirically consistent with the tumor size (pathologic and mammographic) data. This analysis suggested that IL tumors were treated by mastectomy more frequently than were ID tumors (Fig. 6). Although this tendency for mastectomy may be related to the bias of the patient and/or the surgeon, we believe that these procedures were often directed by the pathologic findings. Cancer registry data document that lumpectomy rates for all patients treated at the H. Lee Moffitt Cancer Center are 55% ($n = 1047$). This rate approximates the lumpectomy rate for patients in our study population with ID cancers (56%) yet is significantly different from the lumpectomy rate among patients with IL cancers (40%). Furthermore, a significant number of the IL cancers were treated ini-

tially by lumpectomy but required immediate conversion to mastectomy to achieve clear surgical margins. Table 7 documents a 17.5% conversion rate for IL cancers, whereas only 6.9% of ID cancers required conversion. The rate of ID conversion is spuriously high due to the significant number of patients in this group with DCIS tumor components as well as ID components. These data also speak to the insidious nature of this disease subtype, for which a conversion rate of 9.3% was observed. A relationship may also exist between the age of the patient and the potential need for conversion from planned lumpectomy to mastectomy among the ID group, because the mean age of the patients requiring conversion (48 years) was lower than that of the entire data base (56 years) as well that of ID patients who did not require conversion (56 years). Infiltrating ductal cancers requiring conversion, therefore, may develop in younger, premenopausal patients because of suboptimal mammograms or because the younger patients insist on an attempt at breast preservation despite relative contraindications. This relationship probably does not exist for the IL group, whose mean age is older (age 55). The high rate of conversion in this group is more likely secondary to the biologic characteristic of diffuse infiltration rather than to the poor quality of a premenopausal mammogram.

At the H. Lee Moffitt Cancer Center, preoperative fine-needle aspiration analysis of tumors as well as intraoperative cytologic touch-preparation margin analysis is performed routinely to rapidly and reliably minimize the need for frozen section analysis.[8,15,16] We have demonstrated that the use of diagnostic fine-needle aspiration in a consecutive series of 1875 cases resulted in sensitivity rates of 93.2%, specificity rates of 99.5%, and accuracy rates of 95.6%. In this earlier series, however, IL cancers were extremely difficult to diagnose accurately. In fact, of all 22 cases in which fine-needle aspiration yielded false-negative results, 5 cases (22%) were found to be IL cancers. Similarly, we have demonstrated that touch-preparation margin analysis performed during lumpectomy is generally accurate and reduces duration of surgery as well as overall costs. In a recent report, sensitivity and specificity rates of cytologic touch-preparation analysis were found to be 100% and 96.9% for a group of 162 patients.[16] In the current analysis, however, IL cancers analyzed by the same method were found to have lower rates. In the routine performance of lumpectomy, touch preparations were backed up by intraoperative frozen sections for any IL lesion or for any lesion with dubious margins. All touch-preparation margins were also compared with final permanent histologic margins. Table 8 documents an 11% false-negative rate for IL tumors *versus* 1.0% for ID tumors ($p < 0.0001$). Although false-positive rates were slightly higher for IL tumors, these differences were not statistically significant. Again, these data suggest that lumpectomy for IL cancer must be performed with a low tolerance for conversion to mastectomy.

A comprehensive review of all patients with IL cancer treated at the H. Lee Moffitt Cancer Center confirmed the hypothesis that disease is an insidious variant of breast cancer and is biologically distinct from ID cancer. We have identified a number of biologic determinants that resulted in difficulties with preoperative diagnosis and operative management. The data suggest that although lumpectomy can be performed safely and effectively in selected patients with IL cancer, the decision for lumpectomy as well as the preoperative and intraoperative evaluations must be judicious.

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Discussion

DR. BLAKE CADY (Boston, Massachusetts): I thank Dr. Yeatman and his colleagues for asking me to review this manuscript beforehand. We have all had the feeling that lobular carcinomas sometimes represent a different disease pattern, and it is a service that Dr. Yeatman and his colleagues have defined this for us.

Peculiarities, as he noted, include less mammographic accuracy, larger mean size—although I wonder about median size—higher stage, more frequent node metastases, and a higher proportion with positive margins after lumpectomy, resulting in more mastectomies than in ductal carcinomas.

We noted a higher than expected proportion of invasive lobular cancers in patients with failure to diagnose malpractice actions in a paper representing the occasional obscure clinical presentation of invasive lobular carcinoma without a discreet mass, but a diffuse infiltration of the breast.

Physicians and surgeons, particularly gynecologists, may not be suspicious of cancer while the patient describes a sensation she describes as a mass. This deception is furthered by the frequent negative mammograms and the higher proportion of negative fine-needle aspiration cytology, as reported by the authors. All surgeons need to be aware of this potential for obscure presentation of some diffusely infiltrating lobular carcinomas.

Recent data from the Joint Center for Radiation Therapy in Boston indicate that extensive intraductal component negative breast cancer, and all lobular invasive carcinomas fit into this category because lobular cancer *in situ* has no implications for increased local recurrence in patients, who have focally positive, or even more than focally positive, margins which result in less than 10% local recurrence rate after breast preservation and radiation therapy. They noted specifically that invasive lobular cancers adhere to that data and are as well treated by conservative surgery and radiation therapy as long as the gross mass is totally excised.

Microscopic margins may not be as dangerous as the authors fear, except in that small proportion of infiltrating lobular carcinomas of very diffuse presentation. Thus, it may well be the authors are too cautious regarding the use of lumpectomy and radiation therapy, particularly when, despite poor prognostic features, long-term survival is not different compared with ductal carcinomas. An exception, of course, would be the subset with widespread diffuse presentation.

My questions would be:

What is the rate of in-breast recurrence in their cases comparing invasive lobular and invasive ductal carcinoma? Do they favor neoadjuvant chemotherapy for the large poorly defined diffuse invasive lobular carcinomas once biopsied with proof of the invasive lobular histology before they attempt mastectomy?

Why do invasive lobular carcinomas apparently do better, because this entire group of patients has a more advanced stage and more frequent node metastases, yet the same overall survival? That remains a puzzle. Perhaps it is a different biology, but better than we think. Did a small proportion of very large diffuse invasive lobular carcinomas bias the entire group in terms of their calculation of mean diameter?

I think the authors are to be congratulated for bringing our attention to this unusual type of breast cancer.

DR. JOHN M. DALY (New York, New York): Dr. Yeatman and colleagues are to be commended for their presentation, which combines both a prospective database from their institution along with the tumor registry and shows the power of combining these two to ask questions regarding tumor biology based on clinical observations.

They and others have noted the difficulties in mammographic detection of breast cancers comprised of infiltrating lobular carcinoma. But importantly, they have quantitated the apparent differences in tumor diameters comparing mammography with pathology, which were somewhat larger with the infiltrating lobular compared with infiltrating ductal carcinomas. Immediate recognition of negative margins was also more difficult with the infiltrating lobular compared with the infiltrating ductal carcinoma.

But interestingly, as Dr. Cady pointed out in his question, their patients with infiltrating lobular carcinoma compared with infiltrating ductal had a larger mean tumor size, greater node positivity, greater likelihood of estrogen receptor positivity, and yet they had similar overall survival curves. Is this really true, or does it have something to do with the power of the observation? While having 600-some cases in the infiltrating ductal, they only had 75 in the infiltrating lobular group.

I have several questions for him.

What was the conversion rate from lumpectomy to mastectomy when it was based on tumor size between the two groups rather than the overall conversion rate?

With the higher false-positive margins using both the touch prep cytology and frozen section, do they suggest avoiding the frozen section diagnosis of positive margins except in the most obvious cases?

In patients who underwent mastectomy, do you have information on the incidence of tumor multicentricity in the breast? I also would be interested in the local recurrence rate in the breast after lumpectomy and radiation for all the reasons Dr. Cady pointed out.

Fourth, with similar overall survivals, is this a better disease biologically to have than infiltrating ductal?

Finally, what was the occurrence of bilaterality over time with infiltrating lobular carcinoma, and because of the difficulty to detect this process mammographically how should we follow patients after treatment for their primary tumor?

I enjoyed this presentation by Dr. Yeatman and his colleagues. They have made important observations.