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Report

The influence of infiltrating lobular carcinoma on the outcome of patients treated with breast-conserving surgery and radiation therapy

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Summary

Background: The role of conservative surgery and radiation therapy (CS and RT) in the treatment of patients with infiltrating ductal carcinoma is well established. However, the efficacy of CS and RT for patients with infiltrating lobular carcinoma is less well documented. The goal of this study was to examine treatment outcome after CS and RT for patients with infiltrating lobular carcinoma and to compare the results to those of patients with infiltrating ductal carcinoma and patients with mixed ductal–lobular histology.

Methods: Between 1970 and 1986, 1624 patients with Stage I or II invasive breast cancer were treated with CS and RT consisting of a complete gross excision of the tumor and ≥6000 cGy to the primary site. Slides were available for review for 1337 of these patients (82%). Of these, 93 had infiltrating lobular carcinoma, 1089 had infiltrating ductal carcinoma, and 59 had tumors with mixed ductal and lobular features; these patients constitute the study population. The median follow-up time for surviving patients was 133 months. A comprehensive list of clinical and pathologic features was evaluated for all patients. Additional histologic features assessed for patients with infiltrating lobular carcinoma included histologic subtype, multifocal invasion, stromal desmoplasia, and the presence of signet ring cells.

Results: Five and 10-year crude results by site of first failure were similar for patients with infiltrating lobular, infiltrating ductal, and mixed histology. In particular, the 10-year crude local recurrence rates were 15%, 13%, and l3% for patients with infiltrating lobular, infiltrating ductal, and mixed histology, respectively. Ten-year distant/regional recurrence rates were 22%, 23%, and 20% for the three groups, respectively. In addition, the 10-year crude contralateral breast cancer rates were 4%, 13% and 6% for patients with infiltrating lobular, infiltrating ductal and mixed histology, respectively. In a multiple regression analysis which included established prognostic factors, histologic type was not significantly associated with either survival or time to recurrence.

Conclusions: Patients with infiltrating lobular carcinoma have a similar outcome following CS and RT to patients with infiltrating ductal carcinoma and to patients with tumors that have mixed ductal and lobular features. We conclude that the presence of infiltrating lobular histology should not influence decisions regarding local therapy in patients with Stage I and II breast cancer.

Introduction

The efficacy of conservative surgery and radiation therapy (CS and RT) for the treatment of patients with the most common histologic type of invasive breast cancer, infiltrating ductal carcinoma, has been well established. Infiltrating lobular carcinomas are the second most frequent histologic type of invasive breast cancer. This type of carcinoma is often characterized by insidious infiltration of the breast tissue, which makes it difficult for the mammographer, surgeon, and pathologist to delineate the extent or even the presence of the lesion pre-operatively, at the time of surgery, and during gross examination of the excised breast tissue. In addition, these lesions are often characterized by the presence of multicentricity in the ipsilateral breast [1–5]. These features have raised concerns about the use of CS and RT for patients with infiltrating lobular carcinoma.

Several prior studies, including one from our institution, have suggested that patients with infiltrating lobular carcinoma may be adequately treated with CS and RT [6–16]. The purpose of this study was to evaluate further in a larger population with longer follow-up the treatment outcome of patients with infiltrating lobular carcinoma following CS and RT and to compare these results to those of patients with infiltrating ductal carcinoma and patients with infiltrating carcinoma with mixed ductal and lobular features.

Materials and methods

Between 1970 and 1986, 1624 patients with AJCC-UICC clinical stage I or II invasive breast cancer were treated with CS and RT at the Joint Center for Radiation Therapy (JCRT), Boston, MA. All patients had a complete gross excision of the primary tumor and $\geq$6000 cGy to the primary site. Pathologic material from the primary tumor was available for review in 1337 cases (82%). Of these, 1089 had infiltrating ductal carcinoma and 93 had infiltrating lobular carcinoma (including classical and variant types). Fifty-nine patients had tumors that could not be clearly classified as either infiltrating ductal or infiltrating lobular carcinoma for a variety of reasons. In some of these lesions the tumor cells infiltrated the stroma in a pattern characteristic of infiltrating lobular carcinoma but did not have the cytologic features typical of a lobular cancer. Other lesions were composed of tumor cells that were characteristic of those seen in infiltrating lobular carcinomas, but the pattern of stromal invasion was not typical of any of the variants of infiltrating lobular carcinoma. Therefore, the tumors in these 59 patients were categorized as having mixed ductal and lobular histology. The remaining 96 patients had other histologic types and were excluded from this analysis. The average number of slides available for review was similar for patients in all three groups: 13.3 for infiltrating ductal carcinomas (range 1–76), 13.9 for infiltrating lobular carcinomas (range 1–65) and 11.3 for cancers with mixed ductal and lobular features (range, 2–40). Adjuvant chemotherapy was used in 333 patients, 92% of whom were node-positive. Only 32 patients received adjuvant hormonal therapy (30 with infiltrating ductal carcinoma, one with infiltrating lobular carcinoma, and one with carcinoma with mixed features). The median follow-up time for surviving patients was 133 months.

Histologic features recorded for tumors in all groups included the presence or absence of lymphatic vessel invasion, the presence and extent of associated ductal carcinoma *in situ* and lobular carcinoma *in situ*, and the microscopic margin status. Lymphatic vessel invasion was scored when tumor emboli were noted in thin-walled, endothelial-lined spaces, usually in the peritumoral region. It should be noted that most patients in this series were treated before the evaluation of microscopic margins became routine practice. As a result, microscopic margin status was evaluable in only 400 patients in this series (348 ductal, 28 lobular, and 24 mixed). Among patients with infiltrating lobular and mixed histology, additional features evaluated were the presence or absence of a desmoplastic stromal reaction, the presence of multiple (non-contiguous) foci of invasive carcinoma, and the presence and extent of signet ring cell differentiation in the invasive component of the lesion. Infiltrating lobular carcinomas were further categorized as classical, solid, alveolar, tubulolobular, and pleomorphic subtypes.

The patients in these three groups were compared with regard to their clinical characteristics and treatment outcome. The Fisher exact test was used to compare categorical characteristics between patients with the three histologic types and to compare site of first failure. The log rank test was used to compare time to recurrence and survival between the three groups.

Step-up polytomous logistic regression and proportional hazards regression models were also used to determine which clinical and pathologic features

correlated with site of first failure and time to first failure among the 93 patients with infiltrating lobular carcinoma. Features included in these models were patient's age, T stage, number of positive lymph nodes, use of systemic therapy, year of diagnosis, lobular subtype, lymphatic vessel invasion, multifocal invasion, stromal desmoplasia, stromal reaction at edge of tumor, signet ring cells, and microscopic margin status.

Results

The characteristics of the patients with infiltrating lobular, mixed, and ductal carcinoma are compared in Table 1. Patients with infiltrating lobular carcinoma were significantly older than those with infiltrating ductal or mixed histology. Patients with infiltrating lobular, infiltrating ductal, and mixed histology were similar with regard to the proportion of patients with T1 tumors. Positive axillary lymph nodes and the use of adjuvant chemotherapy were both more common in patients with mixed histology than in patients with ductal or lobular histology. The presence of lymphatic vessel invasion was seen most often in patients with infiltrating ductal carcinoma and least often in patients with infiltrating lobular carcinoma. The presence of positive margins was more common in patients with infiltrating lobular and mixed carcinomas than in patients with infiltrating ductal carcinoma. Among the 93 infiltrating lobular carcinomas 62 were classical, 7 were pleomorphic, 5 were tubulolobular, 3 were alveolar, and 16 had mixtures of classical and other subtypes.

Table 1. Characteristics of patients with infiltrating lobular, mixed, and infiltrating ductal carcinoma

	Histology			
	Lobular	Mixed	Ductal	*p*-value
Number of patients	93	59	1089	
Median age	58	51	50	0.0001
Size T1	55%	57%	56%	0.96
Node+	32%	48%	38%	0.05
LVI+*	15%	27%	38%	<0.0001
Microscopic margins +**	66%	67%	39%	0.0004
Adjuvant chemotherapy	20%	37%	29%	0.07

Abreviation: LVI: lymphatic vessel invasion.
*Among patients evaluable for LVI (88 lobular, 52 mixed, 912 ductal).
**Among patients with evaluable margins (28 lobular, 24 mixed, 348 ductal).

Table 2. Five-year crude results for site of first failure

	Histology		
	Lobular	Mixed	Ductal
Number of patients evaluable	93	59	1082
Alive, NED	75%	68%	67%
Local recurrence	8%	10%	10%
Distant/regional recurrence	13%	14%	16%
Contralateral breast cancer	2%	7%	4%
Dead without recurrence	2%	2%	3%

The *p*-value for the distribution of site of first failure by histologic type was not significant.
Abbreviation: NED, no evidence of disease.

The 5 and 10-year results relating the histologic type to site of first failure are shown in Tables 2 and 3. There were no significant differences among the three groups with regard to local recurrence, distant/regional recurrence, or contralateral breast cancer rates at 5 or 10 years. Furthermore, there were no significant differences in survival in the multiple regression analysis which included established prognostic factors. The hazard ratio was 0.76 for infiltrating lobular versus infiltrating ductal carcinoma ($p = 0.18$) and 0.97 for mixed versus infiltrating ductal carcinoma ($p = 0.91$). Similar results were obtained for time to recurrence.

We also compared the patterns of local recurrence within the breast in patients with infiltrating lobular, infiltrating ductal, and mixed histology carcinomas (Table 4). The patterns of local recurrence within the first five years were similar for patients with infiltrating lobular and infiltrating ductal carcinoma. Among patients with infiltrating lobular carcinoma, six of 7 local recurrences (86%) within the first five years were

Table 3. Ten-year crude results for site of first failure

	Histology		
	Lobular	Mixed	Ductal
Number of patients evaluable	54	31	682
Alive, no evidence of disease	56%	42%	55%
Local recurrence	15%	13%	13%
Distant/regional recurrence	22%	23%	20%
Contralateral breast cancer	4%	13%	6%
Dead without recurrence	4%	10%	6%

The *p*-value for the distribution of site of first failure by histologic type was not significant.

Table 4. Pattern of local recurrence within the first five years related to histologic type

Histologic type	# of LR	Location of LR				
		TR	MM	E	S	U
Lobular	7	4	2	0	1	0
Mixed	6	2	1	1	2	0
Ductal	92	50	22	11	8	1

Abbreviations: LR: local recurrence; TR: true recurrence; MM: marginal miss; E: elswhere in the breast; S: skin of the breast; U: unclassifiable.

Table 5. Crude local recurrence rates for patients with infiltrating lobular carcinoma and infiltrating ductal carcinoma treated with conservative surgery and radiation therapy

Study	Follow-up	Local Recurrence Rates	
		Lobular # pts (%LR)	Ductal # pts (%LR)
Mate[17]	83 mos (med)	12 (25)	108 (13)
White[10]	60 mos (med)	30 (3)	346 (5)
Weiss[9]	61 mos (med)	41 (10)	389 (15)
Schnitt[7]	75 mos (med)	49 (14)	561 (12)
Haffty[14]	126 mos (med)	54 (10)	761 (8)
Poen[8]	66 mos (med)	60 (2)	NA
Bouvet[16]	56 mos (med)	74 (12)	NA
Kurtz[6]	61 mos (med)	67 (18)	709 (11)
Present series	133 mos (med)	93 (15)	1089 (13)
Salvadori[15]	137 mos (med)	286 (8)	1903 (8)
Sastre-Garau[11]*	60 mos (min)	480 (9)	6797 (14)**

*Most patients in this series were treated with conservative surgery and radiation therapy, but some were treated with conservative surgery alone and some were treated with radiation therapy alone.
**This group includes all non-lobular infiltrating carcinomas.
Abbreviation: NA: information not available.

at or near the primary site (either true recurrences or marginal misses). This was comparable to the proportion of local recurrences at or near the primary site within the first five years in patients with infiltrating ductal carcinoma (72 of 92, 78%). Although patients with tumors showing mixed ductal–lobular histology less frequently had recurrences at or near the primary site within the first five years (50%) than patients in either of the other two groups, this may be a reflection of small patient numbers as only six local recurences were observed within the first five years in the mixed histology group.

A polytomous logistic regression model was used to determine the relationship between various clinical and pathologic factors with site of first failure at 5 years (NED vs local vs distant/contralateral/dead of other causes) among patients with infiltrating lobular carcinoma. In that model, higher T stage (T2) was significantly associated with distant failure ($p = 0.01$) and the presence of lymphatic vessel invasion was significantly correlated with the local recurrence ($p = 0.04$). In a proportional hazards model , the presence of four or more positive lymph nodes was the only factor significantly related to time to first failure among patients with infiltrating lobular carcinoma ($p = 0.0001$). It should be noted, however, that the small number of cases and relatively small number of events substantially limited the power to detect differences in these models. Furthermore, although microscopic margin status was not related to the risk of local recurrence among patients with infiltrating lobular carcinoma, microscopic margins were evaluable in only 30% of patients with this histologic type and six of the 7 local recurrences in this group occurred in patients with unevaluable margins.

Discussion

The results of this study indicate that patients with infiltrating lobular carcinoma, infiltrating ductal carcinoma, and carcinomas with mixed ductal and lobular features have similar outcome following treatment with CS and RT with regard to local recurrence, distant/regional recurrence, and survival.

Several pathologic studies have clearly documented that infiltrating lobular carcinomas are frequently characterized by multicentric foci in the ipsilateral breast [1–5]. This observation initially raised concerns about the use of breast-conserving therapy for the treatment of patients with this histologic tumor type. One study that has suggested that infiltrating lobular histology is associated with an increased risk of local recurrence [17]. However, our observations and those of other investigators [6–16] have similarly demonstrated that the risk of local recurrence in patients with infiltrating lobular carcinoma is comparable to that of patients with infiltrating ductal carcinoma and that lobular histology is not a risk factor for local recurrence (Table 5). Furthermore, the pattern of local recurrence in patients with infiltrating lobular carcinoma is similar to that of patients with infiltrating ductal carcinoma (i.e.. most recurrences are at or near the primary site).

There are few available data on the risk of local recurrence in patients whose tumors show mixed ductal and lobular features, since tumors with this histologic appearance are uncommon. This histologic type was

seen in 4.4% of 1337 tumors in our series, in 2.6% of the 879 tumors in the series of Weiss et al. [9], and in 2.2% of the 11,036 tumors in the series of Sastre-Garau et al. [11]. In all three of these studies, the risk of local recurrence in patients with mixed histology was similar to that seen in patients with infiltrating lobular carcinoma and infiltrating ductal carcinoma.

Our results further indicate that infiltrating lobular histology is not a prognostic factor for distant or locoregional recurrence or for overall survival. These results are also similar to the observations of others [6–16]. However, a number of previous authors have noted that the category of infiltrating lobular carcinoma includes a variety of subtypes including classical, alveolar, solid, tubulolobular, and pleomorphic types [18–23]. Moreover, some studies have suggested that patients with the classical pattern of infiltrating lobular carcinoma have a more favorable prognosis than patients with infiltrating ductal carcinoma or with other lobular subtypes [22, 23]. Unfortunately, there were too few patients in our study with lobular subtypes other than the classical subtype to address this interesting issue.

Earlier studies have suggested that patients with infiltrating lobular carcinoma have a frequency of contralateral breast cancer higher than that seen in other histologic types [1, 3, 24]. However, both in our study and in the recent large study by Sastre-Garau et al. [11], the incidence of contralateral breast cancer was similar in patients with infiltrating lobular carcinoma and infiltrating ductal carcinoma.

In summary, our results indicate that patients with infiltrating lobular carcinoma or with carcinomas that show mixed ductal and lobular features have local recurrence and survival rates similar to those of patients with infiltrating ductal carcinoma when treated with conservative surgery and radiation therapy. We conclude that the presence of infiltrating lobular or mixed ductal–lobular histology should not influence decisions regarding local or systemic therapy for patients with Stage I or II breast cancer. In current practice, all resected breast specimens undergo careful assessment for margin involvement and patients with negative margins are considered good candidates for breast conserving therapy, regardless of histologic type. We and others are assessing whether there are subsets of patients with infiltrating ductal and infiltrating lobular carcinoma with limited margin involvement that are also suitable candidates for breast conserving treatment.

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