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Clinical Outcome in Pleomorphic Lobular Carcinoma and Pleomorphic Lobular Carcinoma In-Situ

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Abstract

Aim—Pleomorphic lobular carcinoma (PLC) is a variant of invasive lobular carcinoma (ILC) that is described in the literature as an aggressive tumor with poor prognosis. Multiple studies have shown a decrease in overall survival when compared to classic ILC (cILC). In the current study, we sought to compare the clinicopathologic parameters of PLC to cILC.

Materials and methods—All cases with a diagnosis of ILC, Nottingham grade II-III between 1990 and 2010 were retrieved from the pathology files in the anatomic pathology database at Mayo Clinic in Rochester, MN. The cases were reviewed, and those that met the criteria for pleomorphic lobular carcinoma (PLC) were selected. An E-cadherin immunostain confirmed the lobular immunophenotype. Clinicopathological data was assessed and analyzed. A control group of cILC, Nottingham grade I was selected, comprising two controls for each case, matched according to age and year of diagnosis.

Results—PLC was more associated with in situ carcinoma ($p = 0.03$), and had lower PR expression ($p = 0.03$) when compared to cILC. Both disease-free and overall survival was similar between patients with PLC and matched cILC controls, and depended on disease stage, tumor size and lymph node status.

Conclusion—PLC has a similar behavior to cILC in terms of survival and outcome.

Introduction

Classic invasive lobular carcinoma (cILC) comprises approximately 5-10 % of all invasive mammary carcinomas¹. Most of these tumors are of low grade (usually Nottingham grade 1). However, a small proportion of lobular carcinoma can be of a higher grade and can present with different histologic subtypes including solid, alveolar, histiocytoid, and pleomorphic variants.¹⁻⁴ The pleomorphic variant of lobular carcinoma was described by

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Azzopardi in 1979, and then by Dixon et al in 1982 before it was formally introduced by Page et al. in 1987.^{3, 5-7} PLC is described by the World Health Organization (WHO) classification as a variant of ILC that retains the distinctive growth pattern of lobular carcinoma, but exhibits a greater degree of cellular atypia and pleomorphism than the classical form. It may have signet ring cells, apocrine or histiocytoid differentiation. Many case reviews were reported after that time and all reveal a poor clinical outcome for pleomorphic lobular carcinoma (PLC).⁸⁻¹¹ PLC usually presents at a higher stage, with more lymph node metastasis, and often requires more mastectomy than cILC.⁴ In addition, it has higher rate of distant metastasis.^{2, 4} Many investigators have reported that PLC has worse disease-free survival, advanced stage at presentation, and shorter time to recurrence.^{1, 5, 9, 10} We undertook the current study to investigate the clinical outcome of PLC diagnosed at the Mayo Clinic, Rochester, between 1990 and 2010. The aim of our study was to compare the clinicopathologic parameters and outcome of PLC to the classical variant of ILC.

Material and Methods

Selection of cases and clinicopathologic parameters

Four hundred and eighty nine cases with a diagnosis of ILC Nottingham grade II-III were retrieved from the pathology files of the anatomic pathology database at Mayo Clinic, Rochester, MN, between 1990 and 2010. The hematoxylin and eosin-stained slides were retrieved and reviewed. All cases (total 52) that met the criteria for PLC (Figure 1), were selected and all others were excluded (total 437). An E-cadherin immunostain was performed on all of these cases, and the lobular immunophenotype was confirmed. Clinical data was retrieved, assessed and analyzed for patient age; time of diagnosis; type of surgical treatment; lymph node status; post-surgical treatment including radiation, chemotherapy and HRT; recurrence; and metastasis. Prognostic markers including ER, PR, and HER-2 status as well as history of breast carcinoma other than PLC was also documented when available.

A control group of cILC (Figure 2) was selected, comprised of two controls for each study PLC case (with one exception). The control groups were all cases of cILC, of Nottingham grade I. They were matched to within two years of age in most cases (median difference in age was less than one year) and within two to nine years of diagnosis year (median difference in year was one). The H&E stained slides were reviewed for all controls. Clinical data was retrieved and analyzed for patient age; time of diagnosis; type of surgical treatment; lymph node status; post-surgical treatment including radiation, chemotherapy, and hormonal replacement therapy (HRT); recurrence; and metastasis. Additionally prognostic and predictive markers for ER, PR and HER2 status and a history of breast carcinoma other than lobular carcinoma were documented as well.

Statistical Analysis

Continuous data was summarized with means and standard deviations (or medians and IQR, where appropriate) and was compared between cases and controls with two-sample t-tests or Wilcoxon rank-sum tests, as appropriate. Categorical data was summarized with frequencies and percentages and was compared between cases and controls with chi-square tests or

Fisher's exact tests, as appropriate. Time to event (considering death and recurrence or metastasis) was calculated as the number of years from date of diagnosis to death or first recurrence/metastasis. Those without an event were censored at the date of last follow-up. The risk of each event type was compared with patient characteristics using Cox proportional hazards regression models. Differences in risk were summarized with hazard ratios and 95% confidence intervals. All analyses were conducted using SAS version 9 (Cary, NC). P-values ≤ 0.05 were considered statistically significant.

Results

Clinicopathologic parameters (Table 1)

In our review, PLC has several growth patterns including sheet-like, solid, alveolar, and single file pattern as seen in classical lobular carcinoma. In addition, the cells have moderate to abundant cytoplasm, which may be eosinophilic or amphophilic. There is a moderate to marked degree of nuclear pleomorphism, usually associated with a marked degree of nuclear and cytologic atypia, including enlarged nuclei, nuclear irregularity, hyperchromasia and prominent nucleoli. However, the mitotic activity ranged from low up to high.

Cases and controls were matched in a 1:2 fashion with respect to age and year of diagnosis with one exception. One case was able to be matched with only one control. Almost all (91%) of the case-control pairs were within 2 years apart in age, with a median difference of less than 1 year. Due to difficulty in finding matches for some, we have nine pairs with up to 13 years difference in age. The vast majority (86%) of pairs had diagnosis dates within 2 years of each other, with a median difference of 1 year. Ten pairs were within 3-4 years, three pairs within 7 years, and one pair within 9 years. The average age at diagnosis was 60 years (SD=12.5). PLC and cILC patients were similar with respect to most clinicopathologic characteristics with some exceptions. There was more in-situ carcinoma in PLC than in cILC (70.6% vs 52.4%, $p=0.03$). Patients with cILC tended to have slightly less hormonal treatment than PLC (61.5% vs 75.7%, $p = 0.07$), though this was not statistically significant. Women with PLC will had radiation therapy more often than cILC (51.9% vs 33.0%, $p = 0.02$). Furthermore, the tumors in PLC had less ER (92.2% vs 99.0%, $p = 0.04$) and PR (80.4% vs 92.2%, $p = 0.03$) expression than cILC.

Correlation of survival analysis among cases and controls with other clinicopathologic parameters (Tables 2 and 3)

Among the 52 women with PLC, available follow-up ranged from less than a year to 18.5 years (median 6.1), with 12 women experiencing either a recurrence or metastasis and nine deaths. Among the 103 women with cILC, available follow-up ranged from less than a year to 18.5 years (median 5.3), with 15 women experiencing either a recurrence or metastasis and 18 deaths. In women with PLC, patients' overall survival correlated significantly with surgical treatment (WLE vs. mastectomy), tumor size, disease stage and lymph nodes involvement. Similarly, in women with cILC, overall survival correlated significantly with tumor size and lymph nodes involvement. Disease-free survival correlated significantly with disease stage and lymph nodes' involvement in women with PLC and cILC; in addition, it correlated significantly with tumor size in women with cILC. (Table 3).

Kaplan Meier survival curves for cILC and PLC (figures 3 and 4)

Neither overall survival nor disease-free survival differed significantly between PLC cases and cILC controls. Further, the effects of the clinicopathologic parameters on overall or disease-free survival did not differ significantly between cases and controls.

Discussion

Our study revealed that PLC is not an aggressive variant of ILC when compared to cILC, as described initially by Martinez and Azzopardi in 1979.³ PLC tends to have lower ER and PR expression as compared to cILC, and is more associated with in-situ carcinomas. The behavior of the tumor is dictated by the tumor size, tumor stage and lymph node involvement similar to other conventional types of breast cancer.

Dixon et al., in 1982 studied the different variants of ILC including classical, solid, alveolar and mixed variants.⁵ The classical type was described with single filing growth pattern, with targeted peri-parenchymal distribution, and multifocality.⁵ Like Azzopardi³, they also described the PLC as tumors having a classical architectural pattern with infiltrating trabeculae of cells but with marked nuclear atypia and pleomorphism that is not seen in the classical type.⁵

Moe and Anderson in 2005 studied the proportion of ILC and PLC in the population and found that the proportion of breast cancers with a lobular component increased from 9.5% in 1987 to 15.6% in 1999.¹² Weidner and Semple in 1992 analyzed 16 patients with PLC and concluded that these patients had a poor overall survival when compared to patients with classic type lobular carcinoma.¹¹ Furthermore, they found that PLC is associated with pleomorphic lobular carcinoma in situ in about 45% of cases.¹¹

Eusebi et al. postulated that the aggressive behavior of these tumors could be predicted on the basis of mean tumor size and frequency of nodal metastases.⁹ Similarly, others have found that patients with PLC had high frequency of axillary lymph node involvement.^{10, 13} Likewise, other investigators have found that PLCs presented at an older age group, were larger, with higher histologic grade, more multifocal and multicentric, frequently required mastectomy, had more positive lymph nodes, and developed metastatic disease more often than classical ILC and conventional IDC.¹⁴⁻¹⁶

Middleton et al. analyzed 38 cases of PLC by performing immunohistochemical stains for ER, PR, HER2, p53 and GCDFP15 on 21 cases and studied the loss of heterozygosity for ESR (estrogen receptor gene), p53, HER2 and BRCA1 loci.⁸ In situ components with pleomorphic lobular phenotype was present in 45% (17 of 38 cases), and 21% (8 of 38) had classic lobular in situ (LCIS) components.⁸ The overall five-year survival was 63%. Immunohistochemical analysis revealed that 81% were ER positive, 67% were PR positive, 71% were GCDFP15 positive and 81% were HER2 positive.⁸ LOH was seen in 52% specimens at Tp53 locus, 18% at ESR locus, 24% at HER2 locus and 27-32% at BRCA1 locus.⁸

Radhi et al. studied the immunohistochemical profile of PLC, and they found that these tumors showed chromogranin (3-5%) expression in all cases, as well as p53 expression (range 10-45%) in 50%, and ER and PR immunoexpression in 20%. Whereas cILC showed nuclear p53 expression (5%) and chromogranin (1-2%) expression in 50% of cases each. The authors concluded that p53, ER and PR expression might help predict the degree of aggressiveness of PLCs¹³. Similar to the current study, Bentz. et al and Jacobs et al. has found that PLC s often lacks steroid receptors (ER and PR).^{10, 16}

Frolik et al analyzed the cell kinetics, expression of oncogenes and tumor suppressor genes in 30 cases of PLC and compared these findings with those of poorly differentiated IDC (15 cases) and cILC (15 cases).¹⁷ They found that the PLCs had a lower MIB-1 proliferation index as compared to poorly differentiated IDC.¹⁷ HER2 over-expression and low apoptosis (strong positivity for bcl-2) may be the contributory factor for their aggressive behavior.¹⁷ Furthermore, Jacobs et al. have found that PLC usually has high Ki67 expression as compared to cILC.¹⁶

Palacios et al. in 2003 studied the E-cadherin expression in 29 patients with PLC to see whether these tumors were identical to the cILC or IDC in their phenotype.¹⁸ They observed complete loss of E-cadherin expression in all invasive tumors and also found loss of heterozygosity at 16q22.1 locus (E-cadherin gene locus).¹⁸ Moreover, they showed strong association between loss of E-cadherin immunoexpression and loss of heterozygosity at the same locus.¹⁸ They concluded that these tumors should be considered a variant of lobular carcinoma despite the pleomorphic histology and aggressive behavior.¹⁸

Simpson et al. studied 26 cases of PLC to evaluate whether they are variants of ILC or high grade IDC.¹⁹ They found that PLCs were frequently negative for ER, PR and E-cadherin; and positive for p53 and HER-2 in few cases.¹⁹ The molecular features of PLC were more closely related to ILC (gain of 1q and 16p, loss of 16q and 11q), than high grade IDC, although some of the overlap of molecular alterations that were seen in IDC were also seen in PLC (p53 and HER2 positivity, gain of 8q and 17q24-q25, loss of 13q, amplification of 8q24 [c-myc], 12q14, 17q12 [HER2] and 20q13).¹⁹ These molecular alterations may partially explain the aggressive nature of PLCs.¹⁹

Reis-Filho et al. studied the immunohistochemical and molecular profile of a PLC case and found it lacked E-cadherin and beta-catenin expression, and showed a gain of 1q and a loss of 16q, similar to the cILC, suggesting a common genetic pathway during tumor evolution.²⁰ They also found amplification of c-myc and HER-2, which may be partially associated with the aggressive nature of these tumors.²⁰

Several studies emphasize the fact that PLC is an aggressive variant of ILC with shortened patients' survival and a poor prognosis.^{8-11, 13, 15, 17-20} These tumors usually present at a later stage in the disease process and may have lymph node positive disease.^{9, 10, 13, 14} However, our data suggests that these tumors are not associated with an increased mortality as is described in the literature. In agreement to our study, Jung et al. found that there is no statistical difference on relapse-free and disease-specific survival in patients with PLC when compared to controls with IDC.²¹ Based on genetic pathway

studies, amplifications of c-myc and HER2 detected in PLC may partially account for their more aggressive clinical behavior and the poor outcomes reported in the literature.^{17, 20}

In conclusion, PLC is not an aggressive subtype of breast cancer as previously reported in the literature. Although they might have less ER and PR expression as compared to cILC, they have similar outcome in terms of disease-free and overall survival as compared to cILC.

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Figure 1. Invasive pleomorphic lobular carcinoma with moderate cytologic atypia including nuclear pleomorphism and occasional mitotic activity showing a sheet-like growth pattern (Hematoxylin and eosin, 40×)

Figure 2. Classical invasive lobular carcinoma with mild nuclear pleomorphism and single indian-filing growth pattern (Hematoxylin and eosin, 20×)

Figure 3. Kaplan-Meier plot comparing time to death between cases and controls

Figure 4. Kaplan-Meier plot comparing time to recurrence/metastasis between cases and controls

Table 1
Patient characteristics compared between cases (PLC) and controls (cILC)

	PLC (N=52)	cILC (N=103)	P-value
Age at diagnosis			0.90 ¹
Mean (SD)	60.1 (12.7)	60.4 (12.5)	
Range	(35.3-86.7)	(33.9-85.3)	
Age, category			0.86 ²
33 to <=50	12 (23.1%)	25 (24.3%)	
>50 to <=65	22 (42.3%)	39 (37.9%)	
>65	18 (34.6%)	39 (37.9%)	
Side			0.95 ²
Left	26 (50.0%)	52 (50.5%)	
Right	26 (50.0%)	51 (49.5%)	
Mastectomy	33 (63.5%)	75 (72.8%)	0.23 ²
WLE	19 (36.5%)	27 (26.2%)	0.18 ²
Tumor size, cm			0.81 ³
Median	2.1	2.1	
Q1, Q3	1.3, 4.4	1.2, 4.0	
Tumor size, category			0.95 ²
<=2 cm	25 (49.0%)	51 (49.5%)	
>2 cm	26 (51.0%)	52 (50.5%)	
Stage *			0.42 ²
1	25 (49.0%)	61 (59.2%)	
2	11 (21.6%)	15 (14.6%)	
3/4	15 (29.4%)	27 (26.2%)	
Total lymph nodes			0.83 ³
Median	9.0	7.0	
Q1, Q3	3.0, 17.0	3.0, 18.0	
Number of positive lymph nodes			0.25 ³
Median	1.0	0.0	
Q1, Q3	0.0, 3.0	0.0, 2.0	
Number of positive lymph nodes, category			0.41 ²
0	25 (49.0%)	62 (60.2%)	
1 to <=3	14 (27.5%)	21 (20.4%)	
>3	12 (23.5%)	20 (19.4%)	
% Positive lymph nodes			0.19 ³
Median	4.7	0.0	
Q1, Q3	0.0, 31.3	0.0, 20.0	

	PLC (N=52)	cILC (N=103)	P-value
N stage			0.28 ²
N0	25 (49.0%)	62 (60.2%)	
N1	14 (27.5%)	21 (20.4%)	
N2	3 (5.9%)	10 (9.7%)	
N3	9 (17.6%)	10 (9.7%)	
Multifocal	9 (17.6%)	19 (18.4%)	0.90 ²
Multicentric	4 (7.8%)	20 (19.4%)	0.10 ⁴
In Situ	36 (70.6%)	54 (52.4%)	0.03 ²
LCIS	33 (64.7%)	51 (50.0%)	0.08 ²
DCIS	7 (13.7%)	10 (9.8%)	0.47 ²
LCIS/DCIS, combined			0.23 ⁴
BOTH	4 (7.8%)	6 (5.9%)	
DCIS	3 (5.9%)	4 (3.9%)	
LCIS	29 (56.9%)	45 (44.1%)	
NONE	15 (29.4%)	47 (46.1%)	
LVI	3 (5.9%)	3 (2.9%)	0.40 ⁴
Hormonal tx (yes vs no/na)	32 (61.5%)	78 (75.7%)	0.07 ²
Chemo tx (yes vs no/na)	19 (36.5%)	38 (36.9%)	0.97 ²
Radiation tx (yes vs no/na)	27 (51.9%)	34 (33.0%)	0.02 ²
ER	47 (92.2%)	102 (99.0%)	0.04 ⁴
PR	41 (80.4%)	95 (92.2%)	0.03 ²
HER2	4 (7.7%)	2 (1.9%)	0.10 ⁴

Abbreviations: SD=Standard deviation, Q1=25th percentile, Q3=75th percentile

¹ Equal Variance T-Test

² Chi-Square

³ Wilcoxon

⁴ Fisher Exact

* Stage 3 includes one control patient at stage 4

Note: One patient with diagnosis in 1988 had missing data for most of these characteristics (not included in denominator for many of these percentages).

Table 2
Survival analysis results among cases (PLC) and controls (cILC)

	PLC				cILC			
Variable	N	Events	HR (95% CI)	P	N	Events	HR (95% CI)	P
Age at diagnosis	52	9	1.02 (0.96, 1.09)	0.46	103	18	1.03 (0.99, 1.08)	0.17
Side								
Left	26	3	--	0.33	52	10	--	0.95
Right	26	6	2.02 (0.48, 8.48)		51	8	1.03 (0.40, 2.63)	
Mastectomy								
No	19	1	--	0.04	28	3	--	0.20
Yes	33	8	6.77 (0.81, 56.20)		75	15	2.23 (0.64, 7.71)	
WLE								
No	33	8	--	0.04	76	16	--	0.08
Yes	19	1	0.15 (0.02, 1.23)		27	2	0.29 (0.07, 1.25)	
Size (cm)								
Continuous	51	8	1.18 (0.98, 1.42)	0.07	103	18	1.207 (1.01, 1.44)	0.029
<=2	25	1	--	0.03	51	6	--	0.0372
>2	26	7	7.12 (0.88, 57.89)		52	12	2.75 (1.02, 7.41)	
Stage *								
Continuous	51	8	4.31 (1.53, 12.15)	0.0006	103	18	1.54 (0.89, 2.66)	0.11
1	25	1	--	0.001	61	9	--	0.09
2	11	1	3.18 (0.20, 51.12)		15	2	0.63 (0.13, 2.93)	
3/4	15	6	16.93 (1.99, 143.66)		27	7	2.56 (0.92, 7.15)	
Positive lymph nodes								
Continuous	51	8	1.20 (1.08, 1.33)	<0.0001	103	18	1.11 (1.03, 1.19)	0.004
0	25	1	--	0.008	62	10	--	0.68
>0	26	7	10.30 (1.25, 84.85)		41	8	1.22 (0.48, 3.09)	
% Positive LN (continuous)	49	8	1.04 (1.02, 1.06)	<0.0001	102	17	1.02 (1.01, 1.04)	0.0005
N Stage 3 vs <3								

	PLC				cILC			
Variable	N	Events	HR (95% CI)	P	N	Events	HR (95% CI)	P
N0-N2	42	3	--	<0.0001	93	14	--	0.005
N3	9	5	11.68 (2.69, 50.71)		10	4	4.57 (1.43, 14.60)	
ER								
No	4	1	Insufficient data		1	0	Insufficient data	
Yes	47	7			102	18		
PR								
No	10	2	--	0.38	8	3	--	0.13
Yes	41	6	0.49 (0.10, 2.48)		95	15	0.39 (0.11, 1.36)	
HER2								
No	48	6	Insufficient data		101	18	Insufficient data	
Yes	4	3			2	0		
Multifocal								
No	42	8	Insufficient data		84	14	--	0.45
Yes	9	0			19	4	1.53 (0.50, 4.66)	
Multicentric								
No	47	7	Insufficient data		83	17	--	0.32
Yes	4	1			20	1	0.37 (0.05, 2.81)	
In Situ								
No	15	4	--	0.65	49	10	--	0.73
Yes	36	4	0.72 (0.17, 3.00)		54	8	0.85 (0.33, 2.16)	
LCIS								
No	18	6	--	0.11	51	9	--	0.64
Yes	33	2	0.28 (0.06, 1.44)		51	9	1.25 (0.49, 3.16)	
DCIS								
No	44	6	--	0.30	92	17	--	0.60
Yes	7	2	2.29 (0.46, 11.56)		10	1	0.58 (0.08, 4.41)	

Abbreviations: HR=Hazard ratio, CI=Confidence interval

* Includes 1 control with stage 4

Table 3
Disease-free analysis results among cases (PLC) and controls (cILC)

Variable	PLC				cILC			
	N	Events	HR (95% CI)	P	N	Events	HR (95% CI)	P
Age at diagnosis	52	12	0.98 (0.93, 1.03)	0.41	103	15	1.02 (0.97, 1.07)	0.49
Side								
Left	26	7	--	0.94	52	8	--	0.95
Right	26	5	0.96 (0.30, 3.04)		51	7	1.03 (0.35, 3.03)	
Mastectomy								
No	19	4	--	0.37	28	7	--	0.29
Yes	33	8	1.74 (0.51, 5.91)		75	8	0.57 (0.19, 1.65)	
WLE								
No	33	8	--	0.37	76	9	--	0.29
Yes	19	4	0.58 (0.17, 1.96)		27	6	1.76 (0.60, 5.14)	
Size (cm)								
Continuous	51	11	1.09 (0.92, 1.30)	0.30	103	15	1.236 (1.006, 1.519)	0.04
≤2	25	4	--	0.26	51	6	--	0.30
>2	26	7	1.99 (0.58, 6.85)		52	9	1.75 (0.60, 5.07)	
Stage *								
Continuous	51	11	1.92 (0.97, 3.80)	0.05	103	15	2.72 (1.40, 5.31)	0.001
1	25	3	--	0.14	61	5	--	<0.0001
2	11	3	2.80 (0.56, 13.94)		15	1	Insufficient data	
3/4	15	5	3.83 (0.91, 16.18)		27	9	6.93 (2.09, 22.98)	
Positive lymph nodes								
Continuous	51	11	1.13 (1.04, 1.24)	0.002	103	15	1.15 (1.07, 1.23)	<0.0001
0	25	3	--	0.06	62	6	--	0.21
>0	26	8	3.36 (0.89, 12.74)		41	9	1.94 (0.67, 5.60)	
% Positive LN (continuous)	49	11	1.031 (1.01, 1.05)	0.0003	102	14	1.026 (1.010, 1.042)	0.0004
N Stage 3 vs <3								

	PLC				cILC			
Variable	N	Events	HR (95% CI)	P	N	Events	HR (95% CI)	P
N0-N2	42	7	--	0.03	93	12	--	0.004
N3	9	4	3.57 (1.04, 12.30)		10	3	6.07 (1.50, 24.50)	
ER								
No	4	2	Insufficient data		1	0	Insufficient data	
Yes	47	9			102	15		
PR								
No	10	2	--	0.74	8	3	--	0.12
Yes	41	9	0.77 (0.16, 3.58)		95	12	0.37 (0.10, 1.37)	
HER2								
No	48	10	Insufficient data		101	15	Insufficient data	
Yes	4	2			2	0		
Multifocal								
No	42	10	--	0.69	84	12	--	0.57
Yes	9	1	0.66 (0.08, 5.24)		19	3	1.44 (0.40, 5.18)	
Multicentric								
No	47	11	Insufficient data		83	14	--	0.51
Yes	4	0			20	1	0.51 (0.07, 4.02)	
In Situ								
No	15	5	--	0.69	49	8	--	0.98
Yes	36	6	0.78 (0.23, 2.66)		54	7	1.01 (0.34, 3.01)	
LCIS								
No	18	6	--	0.51	51	7	--	0.74
Yes	33	5	0.66 (0.20, 2.24)		51	7	1.21 (0.40, 3.65)	
DCIS								
No	44	10	--	0.64	92	13	--	0.97
Yes	7	1	0.62 (0.08, 4.84)		10	1	0.96 (0.12, 7.45)	

Abbreviations: HR=Hazard ratio, CI=Confidence interval

* Includes 1 control with stage 4