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Original article

Outcomes of pleomorphic lobular carcinoma versus invasive lobular carcinoma

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ABSTRACT

Purpose: Pleomorphic lobular carcinoma (PLC) is a rare histologic variant of invasive lobular carcinoma (ILC) that has been associated with worse clinical outcomes than classic ILC. Owing to its rarity, high-volume studies of its clinical characteristics and prognosis are lacking. The purpose of this study was to use a large, contemporary cancer database to investigate the clinical characteristics and survival outcomes for patients with PLC.

Methods: The National Cancer Database (NCDB) was queried for women with cT1-4N1-3M0 breast cancer with either ILC or PLC histology having received definitive surgical therapy. Chi-squared analysis was performed to determine differences between the cohorts. Kaplan-Meier analysis evaluated overall survival (OS) between all patients and between patients when stratifying by age and subtype. Cox proportional hazards modeling determined variables associated with OS.

Results: A total of 115,260 patients met the study criteria; of these, 114,859 (99.6%) had ILC, while 401 (0.4%) had PLC. A greater proportion of patients with PLC had T3-4 and node-positive disease, and were more likely to have ER- and HER2+ disease. PLC histology was associated with worse OS on both univariate and multivariate analysis ($p < 0.001$). PLC was associated with poorer OS in subgroups that were T3-4/N+ (but not T1-2N0) disease and ER+ (but not ER-) cancers, but not by HER2 status.

Conclusions: Patients with PLC, who were more likely to have ER- and HER2+ disease, experienced worse OS than patients with ILC, which may be limited to patients with more advanced clinical stage and ER + disease. Further work is needed to determine the optimal treatment for this more aggressive form of breast cancer.

1. Introduction

Pleomorphic lobular carcinoma (PLC) is a rare type of invasive lobular carcinoma (ILC) discovered in 1987 by Davies et al. and further described as a unique histologic entity by Eusebi, Weidener, and Semple [1–3]. Because PLC is a form of ILC, it has some characteristics of ILC such as extensive infiltration of tumor cells into adjacent tissue in the form of single-file lines, localization around terminal ducts in a targetoid pattern, and loss of E-cadherin expression [4–6]. Features that set PLC apart from "classic" ILC include enlarged nuclei with contour irregularities and prominent hyperchromasia; variations in growth to include solid, alveolar, and mixed patterns in a single tumor; and the presence of eosinophilic and granular cytoplasm [1,5]. Additionally, PLC is different from ILC in that it has been known to lose expression of estrogen (ER) and progesterone receptors (PR), and can be associated with HER-2/neu amplification [7]. These unique histopathologic characteristics provide for a more biologically aggressive entity and has been associated with a poor prognosis [7]. The worse outcomes observed in patients with PLC have not been shown to be independently due to histology, and factors such as large tumor size, particular molecular subtypes, and increased metastatic disease may all contribute to the worse outcome observed in these patients [7].

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PLC is estimated to make up around 1% of invasive breast carcinomas and 15% of invasive lobular carcinomas, making it difficult to study and to optimize treatment due to its rarity [7,8]. Earlier studies of small PLC cohorts suggested that this particular carcinoma had worse overall survival (OS) and disease-free survival than invasive ductal carcinomas (IDC) and the "classic" ILC, while other studies found no significant outcome differences [8–10]. More recent studies have suggested that patients with PLC have worse clinical outcomes when compared to patients with IDC [11] or ILC [12], though this did not persist after controlling for stage.

The purpose of the present study was to use a large, contemporary database to further elucidate the clinical characteristics of patients with PLC, as well as to compare the oncologic outcomes between patients diagnosed with PLC and classic ILC.

2. Materials & methods

2.1. Data source and patient selection

The National Cancer Database (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, which consists of de-identified information regarding tumor characteristics, patient demographics, and patient survival for approximately 70% of the US population [13–15]. All pertinent cases are reported regularly from CoC-accredited centers and compiled into a unified dataset, which is then validated. The NCDB contains information not included in the Surveillance, Epidemiology, and End Results (SEER) database, including details regarding use of systemic therapy. The data used in the study were derived from a de-identified NCDB file (2004–2013). The American College of Surgeons and the CoC have not verified and are neither responsible for the analytic or statistical methodology employed nor the conclusions drawn from these data by the investigators. As all patient information in the NCDB database is de-identified, this study was exempt from institutional review board evaluation.

Inclusion criteria for this study were women with newly-diagnosed, T1-4N0-3M0 breast cancer with either the invasive lobular carcinoma histology (International Classification of Disease [ICD]-0-3 codes 8520) or pleomorphic lobular carcinoma histology (ICD-0-3 8022). Cases with unknown information regarding radiation, definitive surgical therapy, and vital status were excluded. In accordance with the variables in NCDB files, information collected on each patient broadly included demographic, clinical, and treatment data.

2.2. Statistical analyses

All statistical tests were two-sided, with a threshold of $p < 0.05$ for statistical significance, and were performed using STATA (version 14, College Station, TX). Survival analysis was per the Kaplan-Meier method, with group comparisons done with the log-rank test. Overall survival (OS) referred to the interval between the date of diagnosis and the date of death, or censored at last contact. Due to imbalance in the two groups of patients, further subset analysis was performed when stratifying patients by stage, tumor markers, and grade. Univariate analysis determined factors associated with overall survival; subsequently, Cox multivariate analysis was performed and included variables that were either significant or showed a strong trend to statistical significance on univariate analysis. The proportional hazards assumption was checked graphically using log-log plots.

3. Results

A flow diagram of patient selection is provided in Fig. 1. A total of 115,260 patients met the study criteria. Of these, 114,859 (99.63%) were diagnosed with classic ILC and 401 (0.35%) with PLC.

Demographic and clinical characteristics are provided in Table 1. No significant differences were observed between patients with ILC and PLC with regards to age, Charlson- Deyo score, income, insurance status, and type of surgical therapy. However, a greater

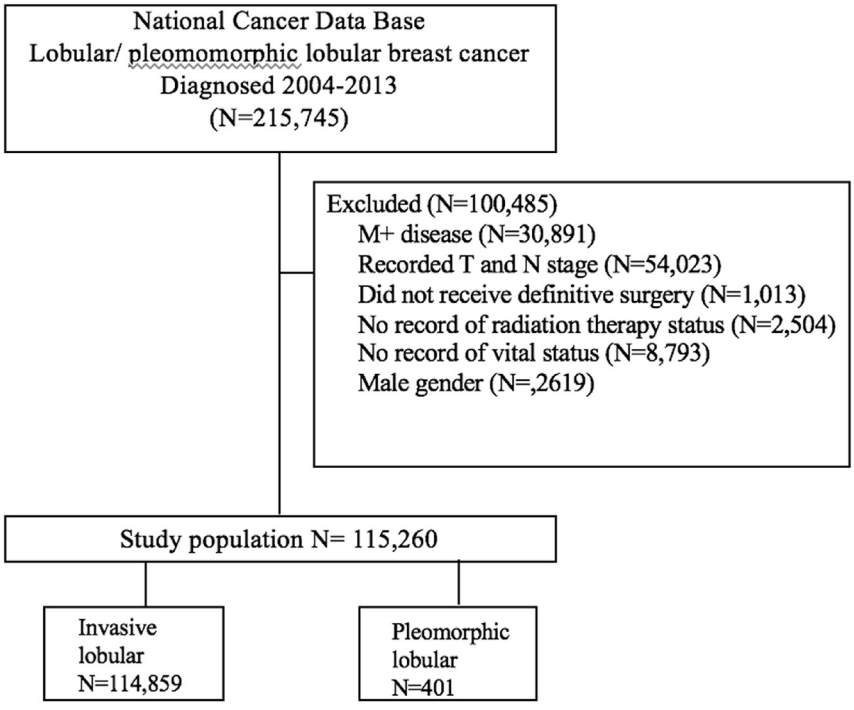

Fig. 1. Patient selection diagram.

Table 1
Demographic and clinical characteristics for all patients.

Characteristic	Invasive lobular n = 114,859 (%)	Pleomorphic Lobular n = 401 (%)	P value
Age			
≤50	20,234 (17.6%)	68 (17.0%)	0.893
51–64	40,622 (35.4%)	140 (34.9%)	
≥65	54,003 (47.0%)	193 (48.1%)	
Race			
White	99,279 (86.4%)	330 (82.3%)	0.003
Black	10,744 (9.4%)	57 (14.2%)	
Other	4836 (4.2%)	14 (3.5%)	
Charlson Deyo Score			
0	97,895 (85.2%)	336 (83.8%)	0.680
1	14,099 (12.3%)	55 (13.7%)	
≥2	2865 (2.5%)	10 (2.%)	
Insurance status			
Medicaid	4643 (4.0%)	26 (6.5%)	0.169
Private	57,433 (50.0%)	193 (48.1%)	
Medicare	48,533 (42.3%)	168 (41.9%)	
Not insured	1559 (1.4%)	6 (1.5%)	
Other	2691 (2.3%)	9 (2.0%)	
Median Income			
≤ $62999	68,637 (59.8%)	247 (61.6%)	0.532
≥ $63000	45,138 (39.3%)	152 (37.9%)	
Not recorded	1084 (0.9%)	2 (0.5%)	
Facility type			
Academic	33,708 (29.4%)	126 (31.4%)	0.001
Nonacademic	79,721 (69.4%)	262 (65.3%)	
Not recorded	1430 (1.3%)	13 (3.2%)	
Year of diagnosis			
2004–2008	50,269 (43.8%)	139 (34.7%)	<0.001
2009–2013	64,590 (56.2%)	262 (65.3%)	
T stage			
T1	62,107 (54.1%)	161 (40.2%)	<0.001
T2	37,374 (32.5%)	12 (40.4%)	
T3	13,718 (11.9%)	67 (16.7%)	
T4	1660 (1.5%)	11 (2.7%)	
N stage			
N0	75,264 (65.5%)	234 (58.4%)	0.003
N1	23,826 (20.7%)	89 (22.2%)	
N2	8869 (7.7%)	40 (10.0%)	
N3	6900 (6.0%)	39 (9.5%)	
Grade			
Well differenitated	28,874 (25.1%)	3 (0.8%)	<0.001
Moderately differentiated	59,053 (51.4%)	154 (38.4%)	
Poorly differentiated/anaplastic	9111 (7.9%)	72 (42.9%)	
Not recorded	17,821 (15.5%)	72 (18.0%)	
Chemotherapy use			
Yes	56,362 (49.1%)	271 (67.6%)	<0.001
No	57,368 (50.0%)	125 (31.2%)	
Not recorded	1129 (1.0%)	5 (1.3%)	
Hormonal therapy use			
Yes	90,571 (79.0%)	248 (61.9%)	<0.001
No	16,838 (14.7%)	131 (32.7%)	
Not recorded	7450 (6.5%)	22 (5.5%)	
Radiation therapy			
Yes	65,315 (56.9%)	239 (59.6%)	0.270
No	49,544 (43.1%)	162 (40.4%)	
ER status			
Positive	108,493 (94.5%)	316 (78.8%)	<0.001
Negative	3156 (2.8%)	79 (19.7%)	
Not reported	3210 (2.8%)	6 (1.5%)	
HER2 status			
Posiive	2333 (2.0%)	33 (8.2%)	<0.001
Negative	49,001 (42.7%)	170 (42.4%)	
Not reported	63,525 (55.3%)	198 (49.4%)	
Surgery			
Lumpectomy	52,143 (45.4%)	185 (46.1%)	0.767
Mastectomy	62,716 (54.6%)	216 (53.9%)	

proportion of PLC patients had T3-4 and/or node positive disease. Additionally, a greater proportion of patients with PLC received treatment at an academic facility. Histologic differences existed between the two groups of patients as well, as PLC patients had a greater proportion of poorly differentiated disease, ER-disease, and tumors that were found to be HER2+. Systemic chemotherapy was used more frequently in PLC patients, while hormonal therapy was used less frequently.

Table 2
Univariate and multivariate analysis for factors predictive of overall survival.

Characteristic	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% confidence interval	P value	Hazard ratio	95% confidence interval	P value
Group						
Pleomorphic lobular	1 (reference)			1 (reference)		
Invasive lobular	0.525	0.430–0.642	<0.001	0.793	0.648–0.971	0.024
Age						
≤50	1 (reference)			1 (reference)		
51-64	1.364	1.285–1.448	<0.001	1.401	1.316–1.492	<0.001
≥65	13.824	3.625–4.035	<0.001	2.846	2.653–3.052	<0.001
Race						
White	1 (reference)			1 (reference)		
Black	1.098	1.046–1.534	<0.001	1.053	1.003–1.107	0.039
Other	0.845	0.779–0.916	<0.001	0.903	0.833–0.979	0.014
Charlson Deyo Score						
0	1 (reference)			1 (reference)		
1	1.915	1.842–1.990	<0.001	1.451	1.396–1.509	<0.001
≥2	3.617	3.394–3.854	<0.001	2.510	2.354–2.676	<0.001
Insurance status						
Medicaid	1 (reference)			1 (reference)		
Private	0.481	0.445–0.520	<0.001	0.595	0.550–0.645	<0.001
Medicare	1.472	1.364–1.588	<0.001	0.830	0.762–0.904	<0.001
Not insured	0.813	0.697–0.948	0.008	0.859	0.737–1.002	0.053
Other/not recorded	0.782	0.689–0.888	<0.001	0.750	0.660–0.853	<0.001
Median Income						
≤ $62999	1 (reference)			1 (reference)		
≥ $63000	0.7	0.679–0.723	<0.001	0.832	0.806–0.860	<0.001
Not recorded	2.628	2.363–2.922	<0.001	2.527	2.271–2.811	<0.001
Facility type						
Academic	1 (reference)			1 (reference)		
Nonacademic	1.252	1.210–1.236	<0.001	1.114	1.076–1.153	<0.001
Not recorded	0.718	0.615–0.838	<0.001	1.398	1.188–1.645	<0.001
Year of diagnosis						
2004–2008	1 (reference)			1 (reference)		
2009–2013	0.913	0.881–0.946	<0.001	1.031	0.982–1.083	0.216
T stage						
T1	1 (reference)			1 (reference)		
T2	1.706	1.650–1.764	<0.001	1.370	1.322–1.421	<0.001
T3	2.418	2.320–2.520	<0.001	1.818	1.734–1.906	<0.001
T4	5.789	5.389–6.219	<0.001	3.008	2.789–3.246	<0.001
N stage						
N0	1 (reference)			1 (reference)		
N1	1.307	1.258–1.358	<0.001	1.439	1.381–1.500	<0.001
N2	2.544	2.434–2.659	<0.001	2.789	2.652–2.932	<0.001
N3	4.106	3.933–4.285	<0.001	4.240	4.031–4.460	<0.001
Grade						
Well differenitated	1 (reference)			1 (reference)		
Moderately differentiated	1.227	1.181–1.275	<0.001	1.134	1.091–1.179	<0.001
Poorly differentiated/anaplastic	1.941	1.841–2.045	<0.001	1.440	1.365–1.520	<0.001
Not recorded	1.229	1.172–1.289	<0.001	1.145	1.092–1.201	<0.001
Chemotherapy use						
Yes	1 (reference)			1 (reference)		
No	1.133	1.101–1.167	<0.001	1.394	1.345–1.444	<0.001
Not recorded	1.022	0.893 = 1.170	0.753	1.106	0.964–1.269	0.152
Hormonal therapy use						
Yes	1 (reference)			1 (reference)		
No	1.84	1.777–1.904	<0.001	1.487	1.431–1.546	<0.001
Not recorded	1.581	1.499–1.667	<0.001	1.545	1.463–1.631	<0.001
Radiation therapy						
Yes	1 (reference)			1 (reference)		
No	1.570	1.525–1.617	<0.001	1.514	1.467–1.563	<0.001
ER status						
Positive	1 (reference)			1 (reference)		
Negative	2.186	2.055–2.325	<0.001	1.526	1.428–1.631	<0.001
Not reported	1.212	1.110–1.324	<0.001	0.970	0.886–1.061	0.504
HER2 status						
Posiive	1 (reference)			1 (reference)		
Negative	0.792	0.690–0.910	0.001	0.896	0.779–1.029	0.120
Not reported	0.896	0.782–1.027	0.115	0.948	0.823–1.092	0.463
Surgery						
Lumpectomy	1 (reference)			1 (reference)		
Mastectomy	1.679	1.628–1.731	<0.001	1.393	1.347–1.441	<0.001

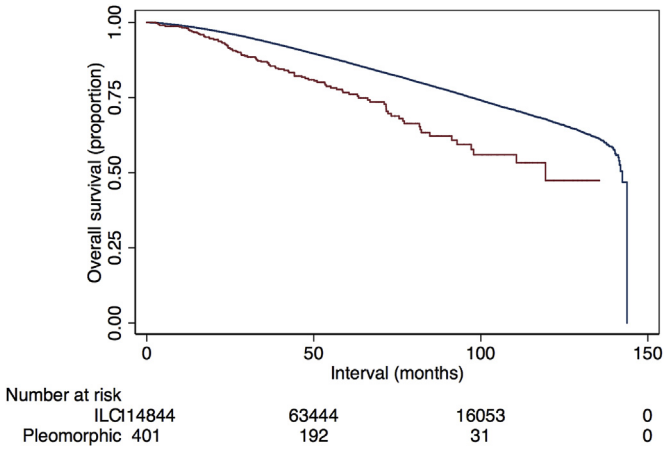

Fig. 2. Kaplan-Meier curves comparing overall survival for all patients.

Results from univariate and multivariate analysis to determine factors associate with OS are displayed in Table 2. PLC histology was found to be associated with worse OS on both univariate and multivariate analysis. Increasing age, Charlson-Deyo scores, T stage, N stage, and poor grade were all associated with worse OS on both univariate and multivariate analysis. Use of chemotherapy, hormonal therapy, and radiation therapy were each associated with improved OS, as was ER positive disease. Her2 positive disease was associated with improved OS on univariate analysis, but not on multivariate analysis.

Fig. 2 displays Kaplan-Meier OS curves based on histology. Amongst all patients, there was superior OS for patients with ILC when compared to patients with PLC (5 year OS 86.7% vs. 76.7%, $p < 0.001$).

On subset analysis, amongst early stage (T1-2N0) patients, no differences were observed OS between patients with PLC and ILC (5 year OS of 90.5% and 89.1%, respectively, $p = 0.108$, Fig. 3A). However, amongst patients with advanced disease (T3-4 or N+), PLC histology was associated with worse OS (5 year OS 64.5% vs. 80.5%, $p < 0.001$, Fig. 3B). Amongst patients with ER + disease, patients with PLC were found to have worse OS (5 year OS 87.3% vs. 68.2%, $p < 0.001$, Fig. 3C), though no significant differences in OS were observed amongst patients with ER-disease (5 year OS 68.6% vs. 69.9%, $p = 0.431$, Fig. 3D). When stratifying by HER2 status, no significant differences were observed between PLC and ILC patients in the two cohorts of patients with either HER2+ ($p = 0.747$) or HER2- ($p = 0.283$) disease (Fig. 3E and F). Additionally, amongst patients with poorly differentiated disease, no significant differences were observed in OS between ILC and PLC patients (5 year OS 78.9% vs. 72.9%, $p = 0.162$, Fig. 3G). Finally, patients with ILC were observed to have superior OS when compared to those with PLC amongst patients undergoing chemotherapy ($p < 0.001$, Fig. 3H) and also amongst patients undergoing hormonal therapy ($p < 0.001$; Fig. 3I).

4. Discussion

The present study is the largest to date describing the clinical characteristics and outcomes associated with PLC. When comparing OS between all PLC and ILC patients, a significantly higher OS was seen in the ILC patients, which is supportive of published works stating that PLC is associated with a worse prognosis [7]. It also differs from those studies that found no difference in OS in PLC patients in comparison to ILC and IDC [6,11,12].

Patients with PLC had more advanced T stage and were more likely to have node positive disease, making it important to analyze the data when stratifying by stage to see if differences in OS would remain. Interestingly, amongst patients with T1-2N0 disease, no significant difference in OS was observed between ILC and PLC patients, while amongst patients with T3-4 or N+ disease, patients with PLC were observed to have worse OS. These results differ from recent studies that found differences in OS attenuated after adjusting for stage [11,12]. The study by Yang et al. compared outcomes between patients with PLC and IDC, which may possibly explain the differences in that study and the present study [11]. The study by Liu et al. did compare outcomes between patients with PLC and ILC, but did not find any differences in outcomes between the two patient cohorts when controlling for stage [12]. However, that study only had a total of 46 patients with PLC, which may have limited the power to detect a statistically significant difference. Therefore, the present results imply that based on histology alone, PLC may be a more aggressive subtype of ILC.

In this study, PLC patients had higher rates of poorly differentiated tumors, ER-disease, and HER2+ disease when compared to patients with ILC, which is consistent with published literature [7]. Because of these findings, further analyses were conducted to investigate differences between PLC and ILC when stratifying for ER status and HER2 status. Amongst patients with ER + disease, PLC patients were observed to have worse OS than patients with ILC disease, suggesting that even patients with ER + PLC may have more biologically aggressive disease than patients with ILC. 8.2% of PLC patients were HER2+ whereas only 2% of ILC patients were HER2+, calling for investigation into OS between PLC and ILC based on HER2 status. OS was not significantly impacted when analyzing by this subtype, though this analysis was limited by the small number of patients for which HER2 status was known.

There are several shortcomings of this investigation, in addition to those present in any retrospective study. First, there is a lack of reporting of histopathological subtype and whether disease was entirely or partially metaplastic, which could influence the natural history and conclusions herein. Second, the NCDB does not keep track of several noteworthy variables, such as other prognostic factors (e.g. lymphovascular space invasion, Ki-67 index), reasons for a particular treatment, premature cessation of therapy, and salvage treatments. Although receipt of chemotherapy is recorded, the number of cycles or specific agents are not mentioned. Importantly, the use of targeted agents such as Trastuzumab and Pertuzumab are not recorded in the NCDB, and therefore an analysis of whether or not these agents work differentially in ILC vs. PLC was unable to be performed. The NCDB also does not record other endpoints such as cancer-specific survival and local/regional control. Nevertheless, the caveats herein do not diminish the need for further investigation to corroborate these conclusions.

5. Conclusions

This is the largest study to date evaluating national practice patterns, clinical characteristics, and outcomes of PLC. PLC was associated with worse OS when compared to ILC in all patients, particularly amongst patients with advanced stage and ER + disease. Further research is needed to confirm these finding in a prospective setting, and to develop therapies that are able to achieve superior outcomes for this aggressive clinical entity.

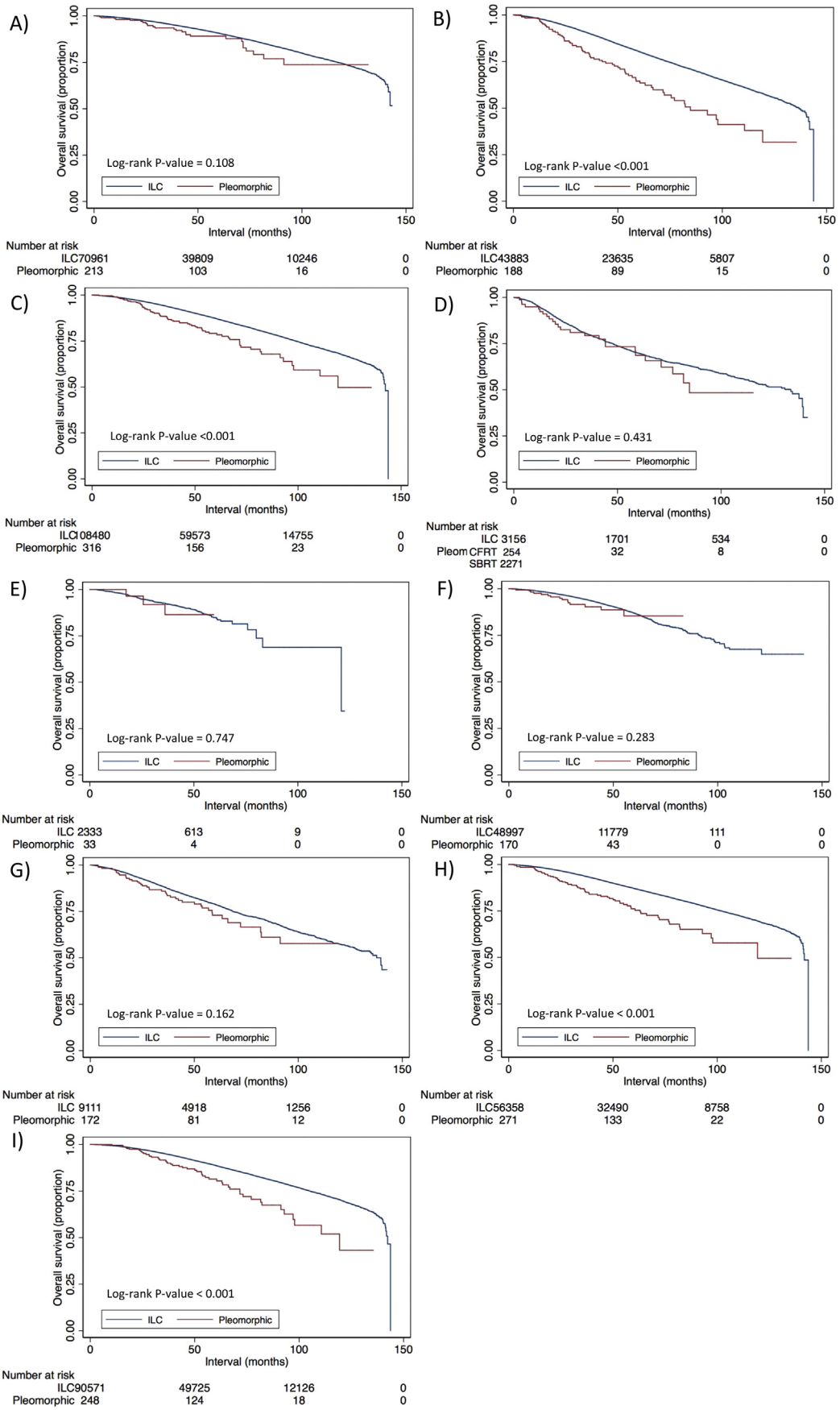

Fig. 3. Kaplan-Meier curves comparing overall survival for patients with A)T1-2N0M0 disease; B) T3-4/N1-3M0 disease; C) Estrogen receptor + disease; D) Estrogen receptor negative disease; E) HER2+ disease; F) HER2-negative disease; G) Poorly differentiated disease; H) Patients receiving chemotherapy; I) Patients receiving endocrine therapy.

Conflicts of interest

The authors have no financial or personal relationships to disclose.

Declaration

There are no acknowledgements. There was no funding for this study. This study has not been presented or published in part or full form elsewhere. All authors declare no conflicts of interest.

Disclaimers

None. This has never been presented/published before in any form. All authors declare that conflicts of interest do not exist.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2018.11.007.

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