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The Real-world Outcomes of Patients With Advanced Invasive Lobular Carcinoma of the Breast Compared With Invasive Ductal Carcinoma: A Review at a Single Institution

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Abstract. *Background: The real-world outcomes of patients with advanced invasive lobular carcinoma (ILC) of the breast are unclear because of its rarity. Patients and Methods: We identified 435 patients with estrogen receptor-positive (ER^+), HER2-negative ($HER2^-$) advanced breast cancer treated at our Institute between 2002 and 2019, and analyzed their outcomes retrospectively. Results: We identified 29 patients with advanced ILC. At presentation, they had a lower rate of lung metastasis (p=0.0053) but a higher rate of stomach metastasis (p=0.0379) compared with other patients with advanced breast cancer. Median overall survival did not differ; however, multivariate analyses showed that ILC histopathology was a risk factor for poorer overall survival (hazard ratio=3.43, p=0.0038) in patients with de novo stage IV ER^+ $HER2^-$ breast cancer. Patients with ILC showed a markedly different patten of subsequent metastasis, such as less in the lung and more in the stomach, leptomeninges, and bone marrow. Conclusion: According to our retrospective study, in patients with de novo stage IV ER^+ $HER2^-$ breast cancer, ILC histopathology was associated with increased risk of death.*

Invasive lobular carcinoma (ILC) of the breast is a relatively rare subtype of breast carcinoma (*i.e.*, up to 10% of breast carcinomas) (1-3); however, its unique behavior in early-stage breast cancer has been investigated (1-6), and treatment strategies for early-stage ILC have been well discussed (2, 7). Most ILCs are of luminal A type biology, being highly estrogen-dependent with relatively indolent growth; however, early-stage ILC may show anatomically extensive lesions at surgery (2, 4, 7), and the prognosis of patients with ILC remains controversial (1, 3, 5, 6, 8). Thus, appropriate surgical removal followed by radiotherapy (if necessary) and perioperative systemic therapy is expected to improve the outcomes of patients with early-stage ILC similarly to those of patients with invasive ductal carcinoma (IDC) (2, 7).

However, because of its rarity and unique behavior compared with early-stage ILC (1, 2, 9-11), the real-world outcomes of patients with advanced ILC have not been well reported, aside from case reports mainly focusing on the unusual presentation of the disease (12, 13). Therefore, the management of advanced ILC is considered relatively difficult, and indeed, some reports have described a poorer outcome for such patients than for those with advanced IDC (4, 5). However, those reports were based on the follow-up of surgical cases, *i.e.*, from the diagnosis of early-stage breast cancer, not from the diagnosis of recurrence or *de novo* stage IV disease.

We therefore retrospectively compared the actual situation of patients with advanced ILC with that of patients with advanced non-ILC breast cancer at a single institution.

Patients and Methods

The medical records of patients with advanced breast cancer who were treated at our hospital from October 2002 to May 2019 were reviewed with the aim of assessing the incidence, background, and outcomes of patients with advanced ILC. The histopathological diagnosis of specimens (primary/metastatic sites) was made by an in-house pathologist. The diagnosis of advanced ILC was made by the presence of typical microscopic findings of hematoxylin-eosin staining, *i.e.*, discohesive feature; therefore, in the study, the immunohistochemical examination of E-cadherin was not mandated for the diagnosis of ILC (2). The estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status was defined

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Key Words: Advanced breast cancer, estrogen receptor-positive, invasive lobular carcinoma, real-world experience.

Table I. *Patient characteristics*.

		Histological group			
		ILC (n=33)	ER+ HER2− ILC (n=29)	ER+ HER2− Non-ILC (n=406)	*p*-Value*
Age at diagnosis, years	Median (range)	60.5 (43-73)	60 (43-70)	54 (26-85)	
Gender, n (%)	Female	33 (100.0)	29 (100.0)	405 (99.8)	
	Postmenopausal	25 (75.6)	20 (69.0)	250 (61.6)	0.5531
	Male	0 (0.0)	0 (0.0)	1 (0.3)	>0.99
Type of breast cancer, n (%)	Advanced	14 (42.4)	11 (37.9)	119 (29.3)	0.4006
	Recurrent	19 (57.6)	18 (62.1)	287 (70.7)	0.4006
Time to recurrence, months	Median (range)	78.3 (24.3-97.2)	81.5 (24.3-97.2)	52.4 (43.4-59.7)	0.3465[a]
Perioperative chemotherapy, n (%)	Yes	17 (89.4)	13 (72.2)	263 (91.6)	**0.0194**
Adjuvant endocrine therapy, n (%)	Yes	-	13 (72.2)	237 (82.6)	0.1757
Receptor status and subtype of ILC, n (%)	ER+ HER2−	29 (87.9)	29 (100.0)	406 (100.0)	
	ER+ HER2+	1 (3.0)	-	-	
	ER− HER2+	0 (0.0)	-	-	
	ER− HER2−	3 (9.1)	-	-	
Involved organ at diagnosis, n (%)	Lung	4 (12.1)	2 (6.9)	122 (30.0)	**0.0053**
	Pleura[§]	3 (9.1)	2 (6.9)	72 (17.8)	0.1984
	Liver	4 (12.1)	4 (13.8)	83 (20.4)	0.4783
	Bone	24 (72.7)	19 (65.5)	226 (55.7)	0.3377
	Skin (regional)[†]	18 (54.5)	15 (51.7)	159 (39.2)	0.5596
	Lymph node (regional)	17 (51.5)	14 (48.3)	238 (58.6)	0.3312
	CNS	0 (0.0)	0 (0.0)	16 (3.9)	0.6144
	Other	5 (15.2)	5 (17.2)	40 (9.9)	0.2062
Number of organs involved	Median (range)	2 (1-8)	2 (1-8)	2 (1-9)	0.5528[b]

CNS: Central nervous system; ILC: invasive lobular carcinoma. §Includes lymphangitis of lung; [†]includes ipsilateral recurrence. *Two-sided Fisher's exact test unless stated otherwise; [a]Log-rank test; [b]Wilcoxon/Kruskal-Wallis test. Statistically significant *p*-values are shown in bold.

according to the guidelines of the American Society of Clinical Oncology/College of American Pathologists (14, 15).

The Fisher's exact test and Wilcoxon/Kruskal–Wallis test were used to assess the distribution of patient parameters. The Kaplan–Meier method was used for the survival analysis, and log-rank test and Wilcoxon's test were used for comparisons between groups. The overall survival (OS) was defined as the period from the diagnosis of advanced breast cancer to death by any cause. For the analysis of risk factors, univariate and multivariate analyses using the Cox proportional hazards model were used. In all statistical analyses, values of $p<0.05$ were considered statistically significant. These statistical analyses were performed using JMP 13.2.0 software program, Japanese version (SAS Institute Inc., Cary, NC, USA).

All procedures performed in studies that involved human participants were in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This retrospective study was approved by the Institutional Review Board of Shizuoka Cancer Center (approval number: T30-25-30-2). Informed consent was obtained in the form of an opt-out option on the hospital website from all individual participants included in the study.

Results

We found data for 706 patients with advanced breast cancer in the database and identified 34 with advanced ILC. Twenty-nine out of the 34 patients with advanced ILC had ER+ HER2− disease, therefore we additionally extracted data for 406 patients with non-ILC, ER+ HER2− advanced breast cancer from the database as a control arm. The median follow-up period was 7.3 years. The breakdown of the patients' background characteristics is shown in Table I.

Histopathological diagnoses. Twenty-nine out of 34 (85.3%) patients with ILC were revealed to have ER+ HER2− disease. The histopathological diagnosis of the primary lesion of these 29 patients was made by in-house pathologists, and the result was as follows: Classic type in 23 (79.3%) and pleomorphic type in six (20.7%), respectively. Presence of signet-ring cells were documented in 8/23 (34.8%) of classic type and 3/6 (50.0%) of pleomorphic type, respectively. Immunohistochemical analyses for E-cadherin were performed on nine specimens (eight classic type and one pleomorphic type), and loss of E-cadherin expression was confirmed in all the specimens. Of the 406 patients with advanced non-ILC ER+ HER2− breast cancer, all were diagnosed as having IDC except for seven patients with mucinous carcinoma.

Characteristics of patients with advanced ER+HER2− breast cancer. As already shown in Table I, patients with advanced

ER^+ $HER2^-$ ILC less frequently received perioperative chemotherapy (72.2% *vs*. 91.6%, p=0.0194) and less frequently had lung metastasis at diagnosis of advanced breast cancer (6.9% *vs*. 30.0%, p=0.0053) than those with advanced ER^+ $HER2^-$ non-ILC according to a two-sided Fisher's exact test. Furthermore, regarding minor metastatic sites, only metastasis to the stomach at the diagnosis of advanced breast cancer was more frequently seen in patients with advanced ILC than in those with advanced non-ILC (p=0.0379, two-sided Fisher's exact test), as shown in Table II.

Table II. *Breakdown of minor sites of metastasis at diagnosis of estrogen receptor-positive human epidermal growth factor receptor 2-negative advanced breast cancer.*

Site of metastasis	ILC (n=29), n (%)	Non-ILC (n=406), n (%)	p-Value*
Adrenal gland	0 (0.0)	4 (1.0)	>0.99
Diaphragm	0 (0.0)	1 (0.2)	>0.99
Kidney	0 (0.0)	1 (0.2)	>0.99
Omentum	2 (6.9)	6 (1.5)	0.0936
Ovarium	1 (3.4)	5 (1.2)	0.3406
Pancreas	1 (3.4)	3 (0.7)	0.2419
Pericardium	0 (0.0)	5 (1.2)	>0.99
Peritoneum	2 (6.9)	6 (1.5)	0.0936
Soft tissue	1 (3.4)	10 (2.5)	0.5361
Skin (distant)	1 (3.4)	9 (2.2)	0.5021
Stomach	2 (6.9)	3 (0.7)	**0.0379**
Thyroid grand	0 (0.0)	1 (0.2)	>0.99
Uterus	1 (3.4)	1 (0.2)	0.1290

ILC: Invasive lobular carcinoma. Some overlapping between cases exists. *Two-sided Fisher's exact test unless stated otherwise. Statistically significant p-values are shown in bold.

Outcomes. As previously described, the distribution of sites of metastasis at the diagnosis of advanced breast cancer was not significantly different, aside from that at the stomach, between the ILC and non-ILC groups (Table II); however, significant, or numerical differences in the subsequent development of metastatic lesions were observed. In addition to presentation at the initial diagnosis of advanced breast cancer, two patients in the ILC group subsequently developed metastasis to the stomach in their clinical course, whereas none in the non-ILC group showed subsequent infiltration into the stomach (p=0.0342, two-sided Fisher's exact test). As we previously reported (16), patients with an ILC histopathology are more likely to develop subsequent central nervous system (CNS) metastasis, including leptomeningeal metastasis (LM). During the observational period, patients in the ILC group showed a trend toward developing LM with or without brain metastasis compared to those in the non-ILC group [5 out of 29 (17.2%) *vs*. 36 out of 405 (8.9%); p=0.1769, two-sided Fisher's exact test], whereas there was no marked difference between the groups in subsequent development of brain metastasis (26.1% *vs*. 30.9%; p=0.8236, two-sided Fisher's exact test). Nine out of 21 (34.5%) deceased patients in the ILC group and 19 out of 273 (7.0%) deceased patients in the non-ILC group were clinically considered to have bone marrow carcinomatosis (BMC), *i.e*., chronic bi- or pan-cytopenia with the appearance of immature blood cells (myelocyte and/or erythroblast) in the peripheral blood, with other myelosuppressive extrinsic stresses able to be ruled out; in addition, the difference was statistically significant according to the two-sided Fisher's exact test (p<0.001).

At the time of data cut-off, 72.4% of patients with advanced ILC and 67.2% of those with advanced non-ILC had died (Table III). The median numbers of chemotherapy regimens applied for advanced breast cancer were not significantly different between the ILC and non-ILC groups (p=0.2525, Wilcoxon/Kruskal-Wallis test), and the median survival from the diagnosis of advanced breast cancer was 44.5 months for the ILC group and 56.2 months for the non-ILC group (Figure 1). There was a strong trend toward an inferior OS for the ILC group compared with the non-ILC group; however, there was no statistically significant difference (p=0.1248, log-rank; p=0.1381, Wilcoxon's test). In the ILC group, there was no marked difference in survival between those with classic type and those with pleomorphic type disease (p=0.5045, log-rank; data not shown). Regarding cause of death, according to definitions previously published (16) (Table IV), patients in the ILC group were less likely to die from respiratory failure than those in the non-ILC group (p=0.0202, two-sided Fisher's exact test); however, no other obvious differences were seen.

We conducted further analyses to identify risk factors for poorer OS from the diagnosis of advanced ER^+ $HER2^-$ breast cancer as shown in Table V, Table VI and Table VII. According to the multivariate Cox regression analyses, the presence of pleural carcinomatosis/pulmonary lymphangitis [hazard ratio (HR)=1.55; 95% confidence interval (CI)=1.11-2.13; p=0.0112], metastasis to the liver (HR=1.85; 95% CI=1.36-2.49; p=0.0001), metastasis to bone (HR=1.54; 95% CI=1.18-2.02; p=0.0016), and metastasis to the CNS (HR=4.05; 95% CI=2.10-7.12; p=0.0001) at diagnosis of advanced breast cancer increased the risk of mortality for patients with ER^+ $HER2^-$ advanced breast cancer (Table V). Furthermore, when limited to patients with *de novo* stage IV disease (N=130; Table VI), ILC histopathology (HR=3.43, 95% CI=1.54-6.84; p=0.0038), the presence of pleural carcinomatosis/pulmonary lymphangitis (HR=2.03, 95% CI=1.13-3.49; p=0.0186), metastasis to the liver (HR=1.90, 95% CI=1.14-3.06; p=0.0147), and metastasis to the CNS (HR=9.69, 95% CI=2.14-31.53; p=0.0062) at diagnosis of advanced breast cancer were identified as risk factors for subsequent poor OS. In contrast, patients in the group with recurrent disease

Table III. *Patient outcomes*.

		Histopathology			
		ER+ HER2−			
		ILC overall	ILC	Non-ILC	*p*-Value*
Number of patients	Total	33	29	406	
Number of chemotherapy regimens	Median (range)	-	3 (0-10)	4 (0-13)	0.2151[a]
Status, n (%)	Alive	8 (24.2)	8 (27.6)	133 (32.8)	
	Died	25 (75.8)	21 (72.4)	273 (67.2)	
	Untraceable	0 (0.0)	0 (0.0)	24 (5.9)	
Cause of death	Cachexia	8 (32.0)	7 (33.3)	68 (24.9)	0.4367
	Respiratory failure	2 (8.0)	2 (9.5)	88 (32.2)	**0.0202**
	Hepatic failure	6 (24.0)	5 (23.8)	77 (28.2)	0.4367
	CNS	5 (20.0)	4 (19.0)	25 (9.2)	0.1393
	Infection	0 (0.0)	0 (0.0)	2 (0.7)	0.99
	Other	4 (16.0)	3 (14.3)	13 (4.8)	0.0961
OS, months	Median OS, months (95% CI)	-	44.5 (32.5-52.7)	56.2 (50.7-65.1)	0.1248[b], 0.1381[c]

CI: Confidence interval; CNS: central nervous system; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; ILC: invasive lobular carcinoma; OS: overall survival. *Two-sided Fisher's exact test unless stated otherwise. [a]Wilcoxon/Kruskal-Wallis test; [b]log-rank test; [c]Wilcoxon test. Statistically significant *p*-values are shown in bold.

(N=305; Table VII) had an increased risk of mortality in cases with a history of adjuvant endocrine therapy (HR=1.76, 95% CI=1.11-2.90; p=0.0150), with a disease-free interval less than 24 months (HR=1.89, 95% CI=1.11-2.90; p=0.0002), and metastasis to the CNS (HR=3.31, 95% CI=1.51-6.45; p=0.0044) at diagnosis of advanced breast cancer.

Discussion

While operable ILC of the breast has been well studied (3, 4-6, 8), the outcome of patients with ILC compared to those with IDC is still controversial. Fritz *et al*. found that histopathological classification, *i.e*., IDC or ILC; did not predict OS (p=0.75, log-rank) from the diagnosis of primary breast cancer in their retrospective cohort study including 14,198 patients with stage I-IV primary breast cancer (17). On the other hand, Pestalozzi *et al*. conducted a large cohort study (13,220 patients with early-stage breast cancer, included 767 with histopathologically confirmed ILC) and found that patients with ER+ ILC (n=586) had an inferior outcome compared with those with ER+ IDC (n=5,123) in terms of disease-free survival (HR=1.30, 95% CI=1.09-1.55) and OS (HR=1.28, 95% CI=1.02-1.62) in the later stage (>6 years for disease-free survival and >10 years for OS) of the follow-up period (1). A similar large cohort study reported by Colleoni *et al*. (18) showed that patients with luminal type ILC had a significantly increased risk of recurrence (HR=1.27, 95% CI=1.05-1.53), distant metastasis (HR=1.48, 95% CI=1.16-1.88), and death (HR=1.34, 95% CI=1.03-1.74) compared with patients with IDC.

Numerous articles, including case reports, focused on the unique clinical presentation of metastatic ILC, such as its unusual metastatic pattern (1, 2, 9-13), have been published. However, the outcomes of patients with advanced ILC have not been well discussed. Inoue *et al*. (19) reported data on 330 patients with advanced breast cancer, including 19 with ILC. In that study, patients with ER+ HER2− ILC (n=16) less frequently had lung metastasis (p<0.01) and more frequently had peritoneal metastasis (p<0.001) than those with ER+ HER2− IDC (n=203); however, no significant difference in the OS between these patients was noted (p=0.53). In our study, no marked difference in the pattern of initial metastasis was found, except for less frequent metastasis to the lung, as in a previous report (20), and more frequent metastasis to the stomach was noted than in the non-ILC group. However, we found that patients in the ILC group were more likely to subsequently develop not only metastasis to the stomach but also accompanying pancytopenia than those in the non-ILC group.

Symptomatic or asymptomatic involvement of the bone marrow by cancer cells can be seen in patients with advanced solid tumors, typically gastric adenocarcinoma (21) and breast cancer (22). Such cases of BMC are clinically characterized by severe thrombocytopenia, refractory anemia, and leukoerythroblastosis, *i.e*., appearance of immature blood cells, typically myelocytes and erythroblasts, in the peripheral blood due to bone marrow infiltration by cancer cells (22). Several reports regarding BMC associated with advanced breast cancer have been published (22-24), and in those

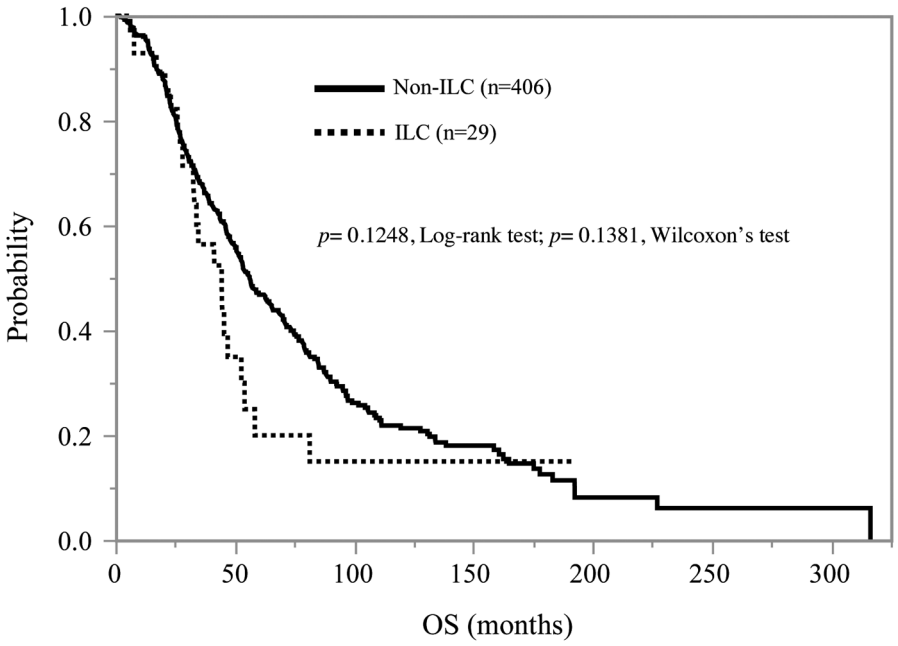

Figure 1. *Kaplan–Meier plots of overall survival (OS) from the diagnosis of advanced breast cancer. ILC: Invasive lobular carcinoma.*

Table IV. *Classification and definitions of cause of death of patients with estrogen receptor-positive human epidermal growth factor receptor 2-negative advanced breast cancer.*

Cause of death		Definition		
1	CNS*	Documented CNS lesion (OR positive for CSF cytology)	AND	Any symptom from CNS lesions (*e.g.*, headache, nausea, focal signs, consciousness disturbance, seizure, neck stiffness) that required medication to relieve
2	Hepatic failure	Documented hepatic lesion	AND	Significant elevations of plasma NH3 and serum bilirubin
3	Respiratory failure	Documented pulmonary/pleural lesion including pulmonary lymphangitis	AND	Continuous requirement of high-flow (≥4 l/min) oxygen therapy
4	Cachexia	Death from cancer	AND	Causes 1-3 were ruled out
5	Infection	Documented severe infection		
6	Other	Death from other than cancer or infection	OR	Unknown details

CNS: Central nervous system; CSF: cerebrospinal fluid; NH3: ammonia. *Applicable when other causes were ruled out.

studies, patients in the ILC group were more likely to show such hematological abnormalities in their later phase of illness than those in the non-ILC group. While no patients underwent a bone marrow biopsy or autopsy to obtain histopathological confirmation of BMC in our study, there were no obvious causes of such hematological abnormalities aside from BMC. Diagnostic imaging, such as radioisotope imaging and magnetic resonance imaging, are useful for detecting BMC (11), and in our study, all patients in the ILC group suspected of having BMC showed typical findings of BMC on radiological imaging. Demir *et al*. (24) reported the median survival time after the diagnosis of apparent BCM was 6.43 months (n=19). Because in our study no patients suspected of having BCM underwent a bone marrow biopsy, we were unable to estimate survival after the development of BCM. Instead, we analyzed the OS from the diagnosis of advanced breast cancer and noted a trend toward an increased risk of death in patients with ILC suspected of having BCM (HR=1.99, 95% CI=0.79-4.91; p=0.142).

Subsequent development of LM is a pattern of CNS metastasis, and patients with advanced ER^+ $HER2^-$ breast cancer with LM have a notably poor outcome (16). In the present study, we showed that an ILC histopathology increased the risk of subsequent development of LM

Table V. *Risk factors for the overall survival from the diagnosis of estrogen receptor-positive human epidermal growth factor receptor 2-negative advanced breast cancer: population overall (n=435).*

Factor	Frequency	Univariate analysis		Multivariate analysis	
	n (%)	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
History/family history/past illness					
Parity	359 (82.5)	1.1698 (0.8647-1.6180)	0.3169		
Family history of cancer	77 (17.7)	0.9682 (0.6974-1.3142)	0.8406		
History of cancer other than BC	58 (13.3)	0.7563 (0.5168-1.0699)	0.1177		
Side of primary lesion (right)	213 (49.0)	0.9190 (0.7308-1.1549)	0.4689		
Background at diagnosis					
Age >64 years	95 (22.5)	0.9118 (0.6733-1.2131)	0.5342		
Menopausal	270 (62.1)	1.1921 (0.9421-1.5152)	0.1441		
De novo stage IV	130 (29.9)	1.0321 (0.7954-1.3269)	0.8092		
ILC histopathology	29 (6.7)	1.4153 (0.8792-2.1542)	0.1456		
Involved organ(s) at diagnosis					
Lung	124 (28.5)	1.1106 (0.8512-1.4343)	0.4335		
Pleura/lymphangitis	74 (17.0)	1.5169 (1.1199-2.0181)	**0.0078**	1.5463 (1.1073-2.1261)	**0.0112**
Liver	87 (20.0)	1.7751 (1.3312-2.3325)	**0.0001**	1.8527 (1.3613-2.4900)	**0.0001**
Bone	245 (56.3)	1.5846 (1.2569-2.0046)	**<0.0001**	1.5416 (1.1776-2.0219)	**0.0016**
Breast/regional skin	174 (40.0)	0.7834 (0.6182-0.9887)	**0.0397**	0.7379 (0.5582-0.9727)	**0.0310**
Locoregional LN	252 (57.9)	1.2317 (0.9772-1.5565)	0.0777		
CNS	16 (3.7)	3.7941 (1.9964-6.5282)	**0.0002**	4.0473 (2.0974-7.1153)	**0.0001**
Other	45 (10.3)	1.2193 (0.8130-1.7582)	0.3245		
>2 Lesions	174 (40.0)	1.3767 (1.0860-1.7393)	**0.0085**	1.0161 (0.7210-1.4227)	0.9266

BC: Breast cancer; CI: confidence interval; CNS: central nervous system; ER: estrogen receptor; HR: hazard ratio; ILC: invasive lobular carcinoma; LN: lymph node. Statistically significant *p*-values are shown in bold.

Table VI. *Risk factors for overall survival from the diagnosis of estrogen receptor-positive human epidermal growth factor receptor 2-negative advanced breast cancer by initial presentation: De novo disease (n=130).*

	Frequency	Univariate analysis		Multivariate analysis	
	n (%)	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Past history/family history/past illness					
Parity	99 (72.6)	1.1302 (0.6843-1.9650)	0.6434		
Family history of cancer	23 (17.7)	1.0471 (0.5636-1.8097)	0.8768		
History of cancer other than BC	20 (15.4)	0.7145 (0.3444-1.3274)	0.3038		
Side of primary lesion (right)	62 (47.7)	1.2040 (0.7796-1.8584)	0.4009		
Background at diagnosis					
Age >64 years	33 (25.4)	1.2299 (0.7368-1.9786)	0.4167		
MenopausaI	80 (61.5)	1.8152 (1.1536-2.9272)	**0.0095**	1.5961 (0.9912-2.6211)	0.0545
ILC histopathology	11 (8.5)	2.8247 (1.2903-5.5121)	**0.0116**	3.4303 (1.5446-6.8387)	**0.0038**
Involved organ(s) at diagnosis					
Lung	38 (29.2)	1.2070 (0.7236-1.9412)	0.4590		
Pleura/lymphangitis	25 (19.2)	2.1357 (1.2254-3.5387)	**0.0087**	2.0310 (1.1320-3.4941)	**0.0186**
Liver	31 (23.8)	1.7245 (1.0411-2.7631)	**0.0349**	1.8994 (1.1406-3.0629)	**0.0147**
Bone	100 (76.9)	1.3198 (0.7903-2.3293)	0.2987		
Breast/regional skin	127 (97.7)	1.3107 (0.2873-23.1955)	0.7796		
Locoregional LN	25 (19.2)	0.9998 (0.5091-2.2621)	0.9996		
CNS	6 (4.6)	8.2144 (1.8769-25.3293)	**0.0088**	9.6884 (2.1413-31.5269)	**0.0062**
Other	18 (13.8)	1.3426 (0.6710-2.4348)	0.3825		
>2 Lesions	105 (80.8)	1.4817 (0.8450-2.8129)	0.1775		

BC: Breast cancer; CI: confidence interval; CNS: central nervous system; CT: chemotherapy; DFI: disease-free interval; ER: estrogen receptor; ET: endocrine therapy; HR: hazard ratio; ILC: invasive lobular carcinoma; LN: lymph node. Statistically significant *p*-values are shown in bold.

Table VII. *Risk factors for overall survival from the diagnosis of estrogen receptor-positive human epidermal growth factor receptor 2-negative advanced breast cancer by initial presentation: Recurrent disease (n=305).*

	Frequency	Univariate analysis		Multivariate analysis	
	n (%)	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Past history/family history/past illness					
Parity	259 (84.9)	1.1787 (0.8088-1.7826)	0.4040		
Family history of cancer	54 (17.7)	0.9340 (0.6289-1.3426)	0.7212		
History of cancer other than BC	38 (12.5)	0.7617 (0.4804-1.1502)	0.2035		
Side of primary lesion (right)	150 (49.2)	0.8414 (0.6402-1.1044)	0.2134		
Background at diagnosis					
Age >64 years	62 (20.3)	0.7713 (0.5226-1.1032)	0.1595		
Menopausal	190 (62.3)	1.0180 (0.7730-1.3475)	0.8998		
De novo stage IV					
Perioperative CT	301 (98.7)	1.8886 (1.1543-3.3427)	**0.0098**	1.0748 (0.5606-2.1303)	0.8308
Adjuvant ET	249 (81.6)	1.7173 (1.2051-2.5193)	**0.0023**	1.7583 (1.1112-2.9045)	**0.0150**
DFI<24 months	74 (24.3)	1.4334 (1.0561-1.9218)	**0.0214**	1.8891 (1.3562-2.6064)	**0.0002**
ILC histopathology	18 (5.9)	1.0593 (0.5588-1.8159)	0.8479		
Involved organ(s) at diagnosis					
Lung	86 (28.2)	1.0711 (0.7790-1.4513)	0.6664		
Pleura/lymphangitis	49 (16.1)	1.3104 (0.9003-1.8544)	0.1532		
Liver	56 (18.4)	1.8673 (1.3024-2.6135)	**0.0010**	1.4324 (0.9691-2.0750)	0.0708
Bone	144 (47.2)	1.6843 (1.2825-2.2131)	**0.0002**	1.5140 (1.1308-2.0297)	**0.0054**
Breast/regional skin	47 (15.4)	0.5311 (0.3511-0.7756)	**0.0008**	0.5532 (0.3620-0.8192)	**0.0026**
Locoregional LN	134 (43.9)	1.2851 (0.9726-1.6931)	0.0774		
CNS	10 (3.3)	3.1474 (1.4841-5.8428)	**0.0045**	3.3073 (1.5071-6.4531)	**0.0044**
Other	26 (8.5)	1.1973 (0.7122-1.8874)	0.4771		
>2 Lesions	69 (22.6)	1.5752 (1.1267-2.1621)	**0.0086**	1.3796 (0.9283-2.0114)	0.1096

BC: Breast cancer; CI: confidence interval; CNS: central nervous system; CT: chemotherapy; DFI: disease-free interval; ER: estrogen receptor; ET: endocrine therapy; HR: hazard ratio; ILC: invasive lobular carcinoma; LN: lymph node. Statistically significant *p*-values are shown in bold.

(HR=2.946; 95% CI 0.990-7.129; p=0.0519) and was identified as an independent prognostic factor for poor OS from the diagnosis of CNS metastasis (HR=3.795, 95% CI 1.167-10.597; p=0.0286). In the ILC group, five out of 29 (17.2%) patients developed LM with or without parenchymal metastasis and had a significantly poorer OS from the diagnosis of advanced breast cancer than those who did not develop LM (median 23.9 *vs*. 47.0 months; p=0.0011, log-rank test; data not shown).

With regard to other causes of death in our study, patients in the ILC group died less frequently due to respiratory failure than those in the non-ILC group (Table III). Patients with advanced breast cancer with ILC histopathology are well known for developing initial metastasis to the lung less frequently than patients with non-ILC (1, 19, 20). Our study showed identical results to previous reports regarding the initial metastatic site, with two out of 29 (6.9%) patients having lung metastasis at the diagnosis of advanced breast cancer, and more interestingly, subsequent metastasis to the lung was documented in two out of 29 patients.

In summary, according to our study, the clinical course of patients with advanced breast cancer with ILC histopathology differs from that of patients with non-ILC histopathology (mainly IDC histopathology) because of its distinct pattern of metastasis that i) less frequently initially involves the lung, and subsequently ii) more frequently involves the stomach initially, iii) more frequently involves the CNS (especially the leptomeninges), iv) more frequently involves the bone marrow; v) furthermore, among patients with *de novo* stage IV ER^+ $HER2^-$ disease, ILC histopathology was an independent negative prognostic factor. Taken together, these findings suggest that a different biology, mainly characterized by dysfunction of E-cadherin, plays a significant role in the development of the unique pattern of metastasis, *i.e*., the loss of E-cadherin promotes epithelial-to-mesenchymal transition, allowing tumor cells to become more migratory and invasive (25). Consequently, diffuse infiltration to organs, *e.g*., BCM or LM, is established and may worsen patient outcome.

Several limitations associated with the present study warrant mention, including its retrospective nature and relatively small number of patients. However, this study is strengthened by its single-institutional setting, as patients were followed-up diligently; in this study, no patient in the ILC group was untraceable, most of the patients who died did so at our hospital with their causes of death identified, and the treatment strategies were consistent.

Conclusion

In summary, according to our retrospective observational study, the outcomes of patients with advanced breast cancer with lobular features were not significantly inferior to those of patients with invasive ductal features; however, in those with *de novo* stage IV disease, ILC histology was identified as a negative prognostic factor. Patients with ILC showed a distinct metastatic pattern not only in the early phase of illness but also in the later phase compared with IDC patients, and a significant proportion of patients with ILC showed leptomeningeal/diffuse bone marrow infiltration that worsened their prognosis. Appropriate management is warranted to improve patient outcomes in the advanced stage, as well as in the early stage of breast cancer, according to the biological features of ILC.

Conflicts of Interest

JW reports having received personal fees from AstraZeneca, Chugai Pharmaceuticals, Daiichi-Sankyo, Eisai Co., Ltd., Eli-Lilly, Novartis Pharma, Pfizer, and Taiho Pharmaceuticals outside the submitted work. SN reports no conflicts of interest.

Authors' Contributions

All Authors contributed to the study conception and design. Material preparation, data collection and data analyses were performed by JW and SN. The first draft of the article was written by JW, and all Authors commented on previous versions of the article. All Authors read and approved the final article.

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