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CLINICAL TRIAL

Analysis of prognosis in different subtypes of invasive lobular carcinoma using the Japanese National Cancer Database-Breast Cancer Registry

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Abstract

Purpose Many studies have shown that the prognosis of invasive lobular carcinoma (ILC) is better than that of invasive ductal carcinoma (IDC). However, both disorders exhibit different prognoses according to molecular subtype, and the prognosis of ILC subtypes might depend on their hormone receptor positivity rate. This study clarified the prognosis of ILC and IDC in each subtype and examined the effectiveness of adjuvant chemotherapy (CT) in luminal ILC.

Methods We planned the analysis using data from the Breast Cancer Registry in Japan. Because it was presumed that there are differences in characteristics between ILC and IDC, we created matched cohorts using exact matching to compare their prognoses. We compared the prognosis of ILC and IDC for each subtype. We also compared the prognosis of luminal ILC between the CT and non-CT groups.

Results For all subtypes, the disease-free survival (DFS) and overall survival (OS) of ILC were poorer than those of IDC. In the analysis by each subtype, no statistically significant difference was found in DFS and OS in luminal human epidermal growth factor 2 (HER2), HER2, and triple-negative cohorts; however, luminal ILC had significantly poorer DFS and OS than luminal IDC. The CT effects on the prognosis of luminal ILC were greater in more advanced cases.

Conclusion Luminal ILC had a poorer prognosis than luminal IDC, contributing to the worse prognosis of ILC than that of IDC in the overall cohort. Different therapeutic approaches from luminal IDC are essential for a better prognosis of luminal ILC.

Keywords Invasive lobular carcinoma · Luminal · Prognosis · Chemotherapy

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Abbreviations

ILC	Invasive lobular carcinoma
IDC	Invasive ductal carcinoma
CT	Chemotherapy
DFS	Disease-free survival
OS	Overall survival
HER2	Luminal human epidermal growth factor 2
JBCR	Japanese Breast Cancer Registry
NCD	National Clinical Database
HR	Hormone receptor
IHC	Immunohistochemistry
ER	Estrogen receptor
PR	Progesterone receptor
TN	Triple-negative
CI	Confidence interval
ET	Endocrine therapy
SEER	Surveillance, Epidemiology, and End Results
RS	Recurrence score

Introduction

Invasive lobular carcinoma (ILC) constitutes 5–15% of all breast carcinomas and its pathological and clinical features differ from those of invasive ductal carcinoma (IDC). ILC is more likely to be low or intermediate grade, hormone receptor-positive, and human epidermal growth factor 2 (HER2)-negative than IDC [1–3]. Therefore, it is considered to have a better prognosis than IDC [1]. Alternatively, recent reports have suggested that the long-term prognosis of ILC is poorer than that of IDC [3–5]. In IDC, prognosis differs widely according to molecular subtype [6]. It has further been reported that each molecular subtype has different outcomes in ILC, as in IDC [7]. Therefore, a better prognosis in ILC might result from the difference in the distribution of molecular subtypes between ILC and IDC. Additionally, the effect of chemotherapy (CT) on ILC has been reported to be inferior to that on IDC [1–3]. However, it is also apparent that the luminal subtype has less chemosensitivity than other subtypes of IDC [8]. Therefore, lower chemosensitivity in ILC might also be related to the higher number of hormone receptor-positive cases in ILC. Overall, how the ILC subtype affects prognosis and chemosensitivity remains unclear. Although ILC is usually not considered a factor in determining treatment, if the prognoses and chemosensitivity of ILC are different from those of IDC, ILC should be approached with different adjuvant therapy. In this study, we compared the prognosis of ILC and IDC for each subtype and examined the effectiveness of adjuvant CT in patients with luminal ILC. As ILC accounts for only a small proportion of breast cancer cases, the data from one institution were insufficient for more accurate analyses. Therefore, we designed the analyses to resolve this issue by using the Japanese Breast Cancer Registry (JBCR), which has collected the clinical information of patients with breast cancer in Japan since 2004 [9, 10].

Methods

Data source

This study was conducted using the JBCR managed by the National Clinical Database (NCD), which is a platform for a nationwide registry in Japan. The Japanese Breast Cancer Society originally managed the registry in 2012 and was supported by the Public Health Research Foundation (Tokyo, Japan) until 2011 [11]. The JBCR contains records of more than 600,000 patients with breast cancer from more than 1,400 institutions in Japan [9]. Affiliated institutions provide data on newly diagnosed primary breast cancers using a web-based system. In addition, the data cover demographic and clinicopathological characteristics; survival data, including disease-free survival (DFS) and overall survival (OS); and therapies, such as types of surgery, CT, endocrine therapy, and radiotherapy. The survival data in the registry were obtained every 5 years from the first treatment, including preoperative therapy and surgery, until 10 years. The TNM classification is registered based on the Unio Internationalis Contra Cancrum system [12], and the histological classification is registered based on the World Health Organization classification [13].

Study patients

Overall, 318,338 patients with breast cancer were registered between 2004 and 2012. We selected 250,736 patients diagnosed with IDC or ILC. Patients with distant metastasis, those who did not undergo surgery, those who received preoperative therapy, and those with bilateral breast cancer were excluded.

Furthermore, hormone receptor (HR) expression was considered positive if at least 1% of nuclei in tumor cells were stained using immunohistochemistry (IHC) for the estrogen receptor (ER) or progesterone receptor (PR). Human epidermal growth factor 2 (HER2) overexpression was defined as IHC 3 + and/or a positive fluorescent in situ hybridization test according to the manufacturer's criteria. Subtypes were categorized as follows: luminal (HR-positive and HER2-negative), luminal HER2 (HR-positive and HER2-positive), HER2 (HR-negative and HER2-positive), and triple-negative (TN) (HR-negative and HER2-negative).

Table 1 Patient characteristics

	IDC		ILC	
	n	%	n	%
Total	130,949		5705	
Age (years)				
< 40	9867	7.53	162	2.84
40 to < 60	61,466	46.94	2699	47.31
60 to < 80	51,835	39.58	2425	42.51
≥ 80	7781	5.94	419	7.34
Menopause status				
Menopause	82,173	62.75	3735	65.47
Pre menopause	43,976	33.58	1775	31.11
Unknown	4800	3.67	195	3.42
Tumor size				
< 2 cm	57,162	43.65	2302	40.35
2 to < 5 cm	60,228	45.99	2635	46.19
≥ 5 cm	9223	7.04	548	9.61
Unknown	4336	3.31	220	3.86
ER				
Positive	100,930	77.08	4950	86.77
Negative	24,529	18.73	578	10.13
Not administered	4834	3.69	168	2.94
No information	656	0.50	9	0.16
PR				
Positive	84,104	64.23	3811	66.80
Negative	41,105	31.39	1707	29.92
Not administered	5065	3.87	178	3.12
No information	675	0.52	9	0.16
HER2				
Positive	19,424	14.83	312	5.47
Negative	96,800	73.92	4887	85.66
Not administered/No information	14,725	11.24	506	8.87
Number of lymph node metastases				
None	84,565	64.58	3580	62.75
1 to 3	29,511	22.54	1158	20.30
4 to 9	7857	6.00	386	6.77
≥ 10	3672	2.80	362	6.35
Not administered/No information	5344	4.08	219	3.84
Initial surgical treatment				
Mastectomy	53,329	40.73	3109	54.50
Breast-conserving surgery	77,620	59.27	2596	45.50
Endocrine therapy				
Yes	92,661	70.76	4616	80.91
No	38,288	29.24	1089	19.09
Chemotherapy				
Yes	57,290	43.75	2245	39.35
No	73,659	56.25	3460	60.65
Radiotherapy				
Yes	64,603	49.33	2490	43.65
No	65,848	50.29	3189	55.90
No information	498	0.38	26	0.46

ILC, invasive lobular carcinoma; IDC, invasive ductal carcinoma; HER2, luminal human epidermal growth factor 2; ER, estrogen receptor; PR, progesterone receptor

Outcome

DFS and OS were the primary outcomes of this study. DFS was defined as the interval between the date of surgery and the time of local or distant recurrence or death from any cause. OS was defined as the time interval between the date of surgery and the date of death from any cause.

Statistical analysis

We tabulated the clinicopathological features of the patients with IDC and ILC. To evaluate the prognosis of each subtype, we compared DFS and OS for IDC and ILC in an exactly matched cohort based on patient age, menopausal status, tumor size, ER, PR, HER2, lymph node status, and initial surgical treatment at a 1:1 ratio. Survival curves were constructed using the Kaplan–Meier method, and prognoses were compared using the log-rank test. Cox proportional hazards model was used to estimate the hazard ratios and 95% confidence intervals (CIs) for survival.

Furthermore, to evaluate the chemosensitivity of luminal ILC, we selected patients with pT2N0M0 or pT1-2N1M0 ILC who underwent mastectomy and endocrine therapy. Patients were categorized into an endocrine therapy-only group (ET) and an endocrine therapy and CT group (ET + CT). They were matched based on their age group, menopause status, tumor size, ER and PR status, and use of post-surgery radiotherapy at a 1:1 ratio. We compared the DFS and OS between the two groups.

All tests were two-sided, and statistical significance was set at a $p < 0.05$. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Overall, 207,428 patients were enrolled after selection based on the inclusion and exclusion criteria. Of these, 10-year follow-up data were available for 136,654, and we examined 130,949 cases of IDC and 5,705 cases of ILC.

Compared with IDC tumors, the ILC tumors tended to be larger, and more often hormone receptor-positive and HER2-negative (Table 1). ILC was also associated with lymph node positivity.

Prognosis for each molecular subtype

After matching, we identified 5,633 patients with IDC and 5,633 with ILC for prognostic analysis (Fig. 1; Table 2). For all subtypes, the 10-year DFS rate was 79.1 and 76.6%

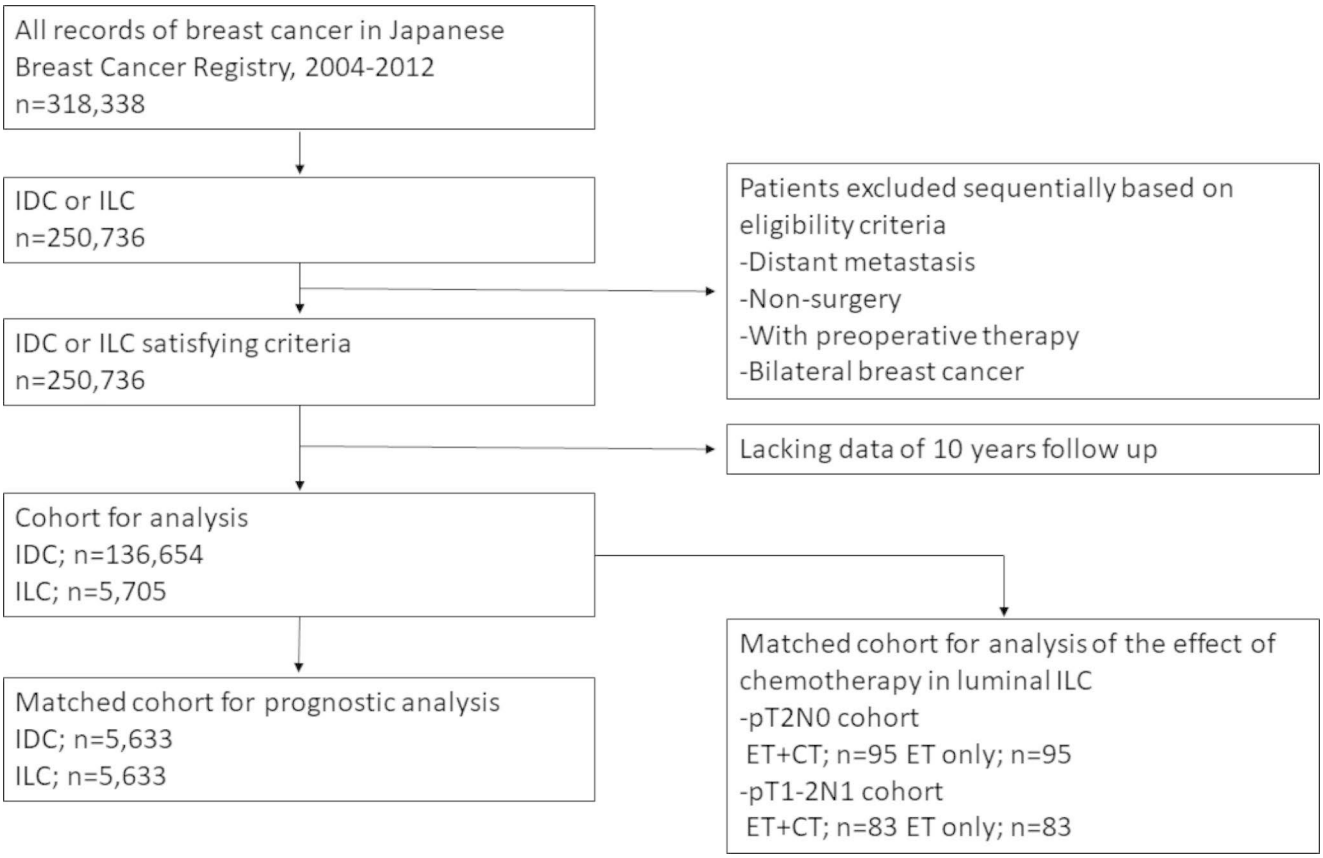

Fig. 1 Consort diagram of this study. IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ET, endocrine therapy; CT, chemotherapy

in IDC and ILC, respectively ($p=0.04$; hazard ratio, 1.10 [95%CI, 1.00–1.21]) (Fig. 2). The 10-year DFS rates in the IDC and ILC groups were 81.2 and 78.0% in the luminal group ($p=0.01$; hazard ratio, 1.16 [95%CI, 1.04–1.30]), 75.0 and 71.1% in the HER2 group ($p=0.72$; hazard ratio, 1.13 [95%CI, 0.59–2.1], 74.3 and 73.2% in the luminal HER2 group ($p=0.81$; hazard ratio, 0.95 [95%CI, 0.62–1.45]), and 62.6 and 67.7% in the TN group ($p=0.21$, hazard ratio, 0.86 [95%CI, 0.67–1.09]), respectively (Fig. 3).

The 10-year OS rate was 87.2 and 84.7% for IDC and ILC, respectively, for all subtypes ($p<0.01$; hazard ratio, 1.23 [95%CI, 1.09–1.39]) (Fig. 2). The 10-year OS rates in IDC and ILC were 89.1 and 86.0% in the luminal group ($p<0.01$; hazard ratio, 1.42 [95%CI, 1.22–1.65]), 78.2 and 86.4% in the HER2 group ($p=0.35$; hazard ratio, 0.67 [95%CI, 0.29–1.57]), 81.1 and 85.9% in the luminal HER2 group ($p=0.74$; hazard ratio, 0.91 [95%CI, 0.52–1.59]), and 70.4 and 73.0% in the TN group ($p=0.28$; hazard ratio, 0.86 [95%CI, 0.65–1.13]), respectively (Fig. 4).

The effects of CT

Among patients with ILC who underwent mastectomy and endocrine therapy, we identified 332 and 113 patients with pT2N0 who underwent ET only and ET + CT treatment, respectively. In addition, 130 and 185 patients with pT1-2N1 underwent ET only and ET + CT treatment, respectively. After matching, we identified 95 pairs of ET + CT and ET-only patients in the pT2N0 cohort (Table 3) and 83 pairs in the pT1-2N1 cohort (Table 4).

In the pT2N0 cohort, the 10-year DFS rate was 82.1 and 87.4% in the ET + CT and ET-only groups, respectively ($p=0.99$; hazard ratio, 1.00 [95% CI, 0.42–2.42]). The 10-year OS rate of the ET + CT and ET-only groups was 93.5 and 94.0%, respectively ($p=0.89$; hazard ratio, 1.10 [95% CI, 0.29–4.11]). In the pT1-2N1 cohort, the ET-only and ET + CT groups had a 10-year DFS rate of 54.2 and 77.0%, respectively ($p=0.35$; hazard ratio, 0.72 [95% CI, 0.36–1.44]). The 10-year OS rate in the ET-only and ET + CT groups was 62.0 and 94.8%, respectively ($p=0.01$; hazard ratio, 0.25 [95% CI, 0.08–0.78]) (Fig. 5).

Discussion

Our study showed that the DFS and OS of ILC were lower than those of IDC in the overall cohort. Furthermore, luminal type accounted for most of the overall cohort, and the

Table 2 Patient characteristics of the matched cohort for comparing prognoses between ILC and IDC

	IDC		ILC	
	n	%	n	%
Total	5633		5633	
Age (years)				
< 40	152	2.70	152	2.70
< 60	2673	47.45	2673	47.45
< 80	2407	42.73	2407	42.73
≥ 80	401	7.12	401	7.12
Menopause status				
Menopause	3702	65.72	3702	65.72
Pre menopause	1750	31.07	1750	31.07
No information	181	3.21	181	3.21
Tumor size				
< 2 cm	2280	40.48	2280	40.48
2 to < 5 cm	2612	46.37	2612	46.37
≥ 5 cm	534	9.48	534	9.48
No information	207	3.67	207	3.67
ER				
Positive	4910	87.16	4910	87.16
Negative	566	10.05	566	10.05
Not administered/No information	157	2.79	157	2.79
PR				
Positive	3793	67.34	3793	67.34
Negative	1678	29.79	1678	29.79
Not administered/No information	162	2.88	162	2.88
HER2				
Positive	304	5.40	304	5.40
Negative	4845	86.01	4845	86.01
Not administered/No information	484	8.59	484	8.59
Lymph node status				
None	3561	63.22	3561	63.22
1 to 3	1152	20.45	1152	20.45
4 to 9	373	6.62	373	6.62
≥ 10	340	6.04	340	6.04
Not administered/No information	207	3.67	207	3.67
Initial surgical treatment				
Mastectomy	3053	54.20	3053	54.20
Breast-conserving surgery	2580	45.80	2580	45.80
Endocrine therapy				
Yes	4407	78.24	4566	81.06
No	1226	21.76	1067	18.94
Chemotherapy				
Yes	2216	39.34	2205	39.14
No	3417	60.66	3428	60.86
Radiotherapy				
Yes	2433	43.19	2459	43.65
No	3188	56.60	3149	55.90
No information	12	0.21	25	0.44

ILC, invasive lobular carcinoma; IDC, invasive ductal carcinoma; HER2, luminal human epidermal growth factor 2; ER, estrogen receptor; PR, progesterone receptor

DFS and OS of luminal ILC were lower than those of luminal IDC. Our results were consistent with the findings of recent reports that the long-term prognosis for ILC is poorer than that for IDC [3–5], and further revealed that the poor prognosis in ILC is because the prognosis of ILC is poorer than that of IDC in the luminal type, which accounts for most ILC. In comparison, no consistent results were found for DFS or OS in the luminal HER2 and HER2 groups. In the TN group, the DFS of IDC was lower than that of ILC, and the same result was observed for OS. However, the limited number of patients may have led to the lack of statistically significant differences. Therefore, further studies with larger data are needed to clarify the prognosis of the luminal HER2, HER2, and TN cohorts.

Several studies have compared survival between IDC and ILC regarding overall subtypes. However, few have compared the prognosis between IDC- and ILC-stratified subtypes. For example, Yang et al. [14] used the Surveillance, Epidemiology, and End Results (SEER) database and compared the prognosis between 29,199 IDC and 29,199 ILC cases selected using propensity score matching. They found that ILC had no difference in prognosis from IDC in a hormone receptor-positive cohort. In contrast, the prognosis of ILC was poorer than that of IDC in the hormone receptor-negative cohort. This study used the largest data of any study comparing IDC and ILC according to hormone receptor positivity; however, some HER2 data are missing. Furthermore, Xiao et al. [15, 16] and Chen et al. [16] used the SEER database to compare the prognosis of IDC and ILC in groups categorized using hormone receptor status. Both studies reported that ILC had a poorer prognosis than IDC in the hormone receptor-positive group. Moreover, Pestalozzi et al. [4] demonstrated that the prognosis of ER-positive ILC worsened 6 years after diagnosis, using data from 15 International Breast Cancer Study Group trials. Nevertheless, they also lacked information regarding HER2 expression.

However, as HER2 is an important prognostic factor in breast cancer, HER2 status should also be considered. Accordingly, Lim et al. [17] used the Korean Breast Cancer Registry to examine the survival of IDC and ILC for each subtype. To the best of our knowledge, this is the first study comparing the prognosis of IDC and ILC according to the subtype; specifically, they concluded that IDC and ILC had similar prognoses for each subtype. Notably, this study did not adjust for clinicopathological differences between ILC and IDC, such as tumor size. Engstrøm et al. [18] concluded that luminal ILC with histopathological grade 2 had a poorer prognosis than luminal IDC with histopathological grade 2, even after adjusting for age and stage. Notably, these findings are consistent with those in the present study, although only grade 2 ILC was evaluated and the number

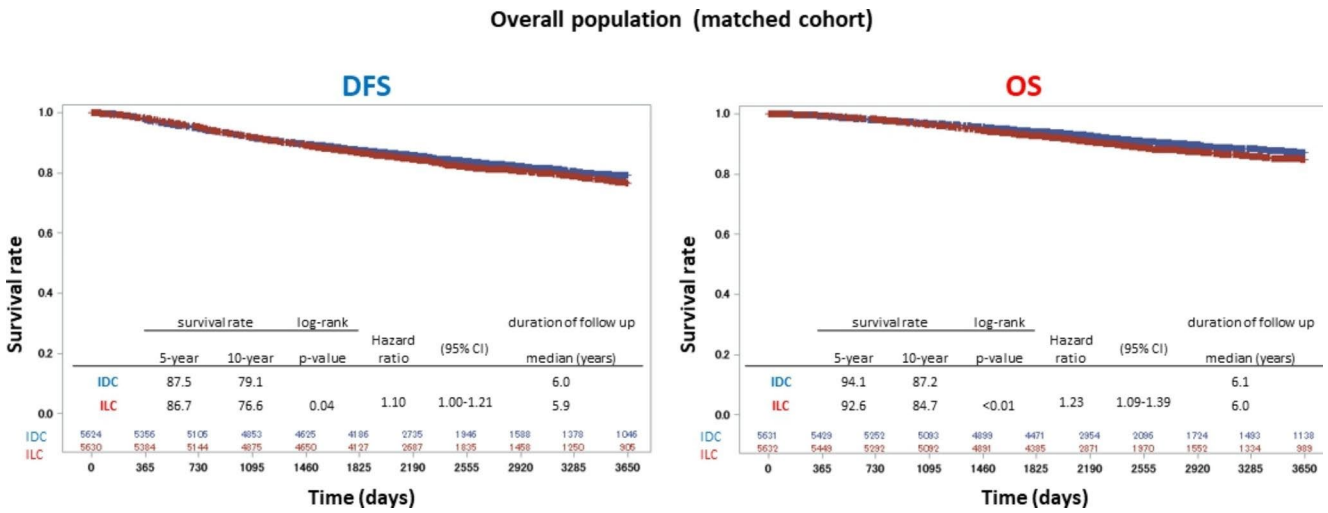

Fig. 2 Prognosis of ILC and IDC. ILC, invasive lobular carcinoma; IDC, invasive ductal carcinoma; OS, overall survival; DFS, disease-free survival

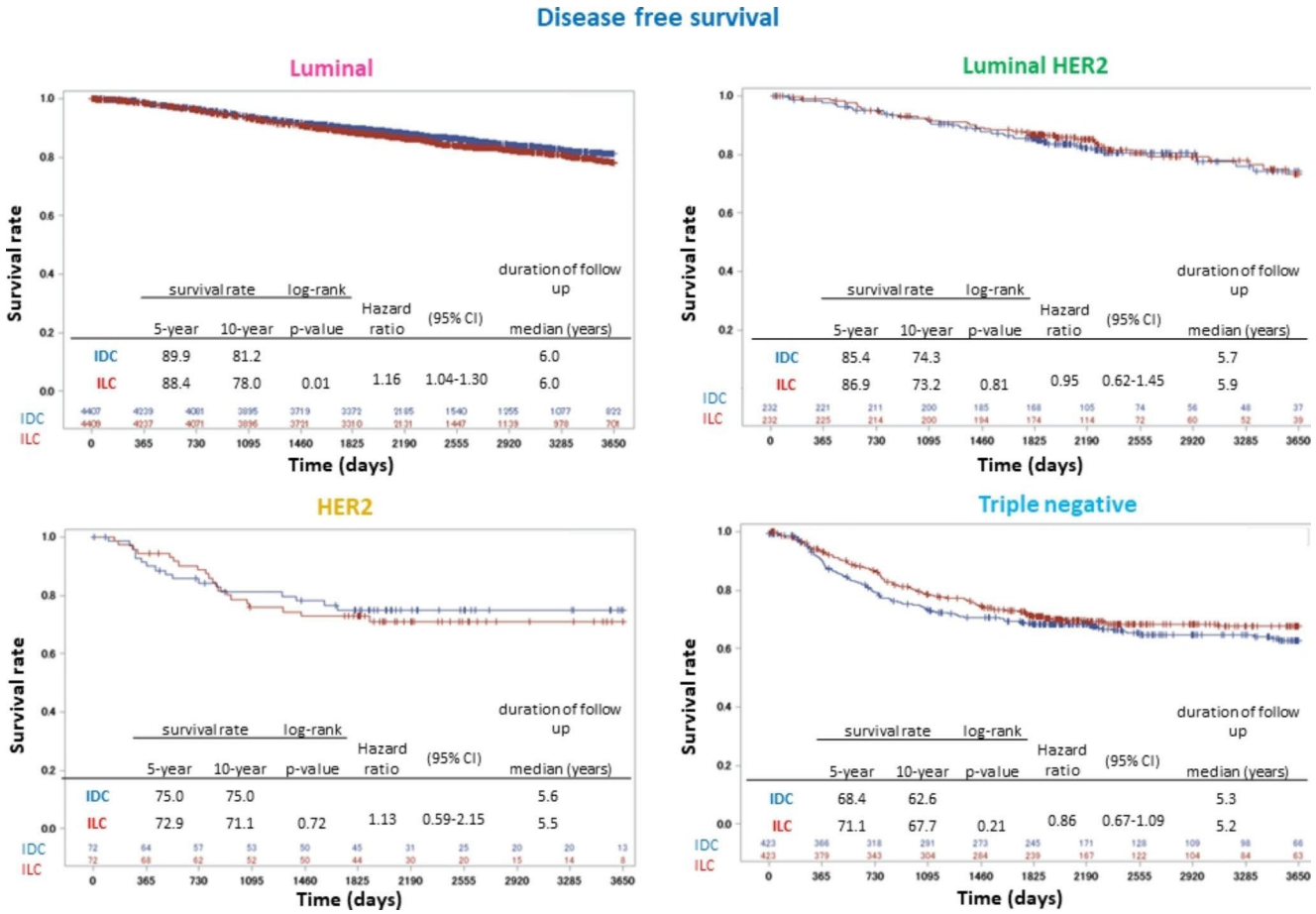

Fig. 3 Disease-free survival of ILC and IDC in each subtype. ILC, invasive lobular carcinoma; IDC, invasive ductal carcinoma; HER2, luminal human epidermal growth factor 2

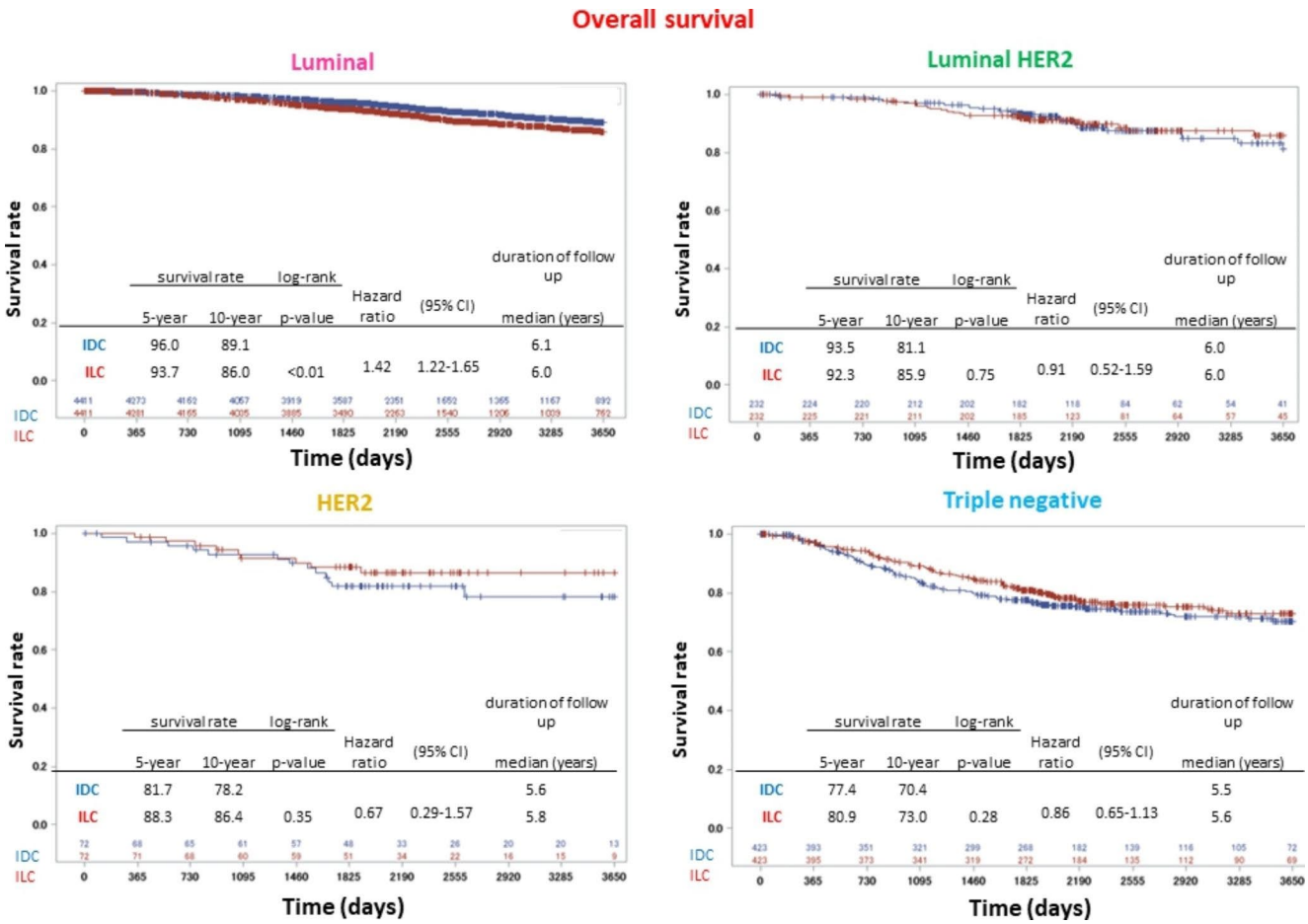

Fig. 4 Overall survival of ILC and IDC. ILC, invasive lobular carcinoma; IDC, invasive ductal carcinoma; HER2, luminal human epidermal growth factor 2

of cases was small [18]. In the most recent report, Weiser et al. [19] found that the 5-year OS did not differ between the luminal ILC and IDC in multivariable Cox analysis using the National Cancer Database in the United States. The different results from our study might be because we compared the 10-year prognosis as luminal breast cancer has an indolent course, whereas they compared the 5-year prognosis. Overall, to our knowledge, our study represents the largest data set followed over a long period that compares IDC and ILC with adjusted HR, HER2, and clinicopathological backgrounds. Consequently, we could conclude that the prognosis for luminal ILC was worse than that for luminal IDC, which resulted in a poorer prognosis for ILC, even in the overall cohort.

The reason for the worse prognosis in luminal ILC may arise from different genomic profiles. It has been reported that ILC has more ERBB2 and FOXA1 mutations than IDC [20], and they are associated with endocrine resistance [21]. Moreover, more than 50% of metastatic ILC have at least one mutation associated with endocrine therapy resistance, such as mutations in AKT1, ARID1A, ESR1, NF1, or PTEN, in addition to mutations in ERBB2 and FOXA1 [20, 21]. Recently, some clinical data have also suggested that there are differences in the association between endocrine therapy and histological subtypes, ILC and IDC. For example, Filho et al. [22] suggested that adjuvant letrozole is more beneficial than tamoxifen in patients with ILC. In addition, Strasser-Weippl et al. [23] reported that ILC had a better prognosis when treated with anastrozole than with exemestane, whereas no difference was found in IDC treatment. Therefore, differentiating endocrine therapy from IDC might be an innovative approach to extending the prognosis of ILC.

In this study, we investigated the efficacy of CT for luminal ILC in patients with pT2N0M0 or pT1-2N1M0 disease. CT improves the prognosis of luminal ILC only in pT1-2N1M0 patients. Although there are many reports that CT does not improve the prognosis of ILC due to the high positivity of hormone receptors, there are few reports regarding the efficacy of CT on luminal ILC. For example, Marmur et al. [24] examined the efficacy of CT in stage I/II luminal ILC using data from the California Cancer Registry. They concluded

Table 3 Patient characteristics of the matched cohort for examination of the effects of chemotherapy in pT2N0 luminal ILC

	Pre matching				Post matching			
	Chemotherapy		No-chemotherapy		Chemotherapy		No-chemotherapy	
	n	%	n	%	n	%	n	%
Total	113		332		95		95	
Age (years)								
< 20	0	0.00	1	0.30	0	0.00	0	0.00
20–29	0	0.00	0	0.00	0	0.00	0	0.00
30–39	9	7.96	2	0.60	2	2.11	2	2.11
40–49	27	23.89	50	15.06	23	24.21	23	24.21
50–59	27	23.89	50	15.06	23	24.21	23	24.21
60–69	30	26.55	95	28.61	29	30.53	29	30.53
70–79	18	15.93	92	27.71	16	16.84	16	16.84
≥ 80	2	1.77	42	12.65	2	2.11	2	2.11
Menopause status								
Menopause	71	62.83	260	78.31	63	66.32	63	66.32
Premenopause	42	37.17	72	21.69	32	33.68	32	33.68
Tumor size								
< 2 cm	0	0.00	0	0.00	0	0.00	0	0.00
≥ 2 cm	113	100.00	332	100.00	95	100.00	95	100.00
ER								
Positive	109	96.46	332	100.00	95	100.00	95	100.00
Negative	4	3.54	0	0.00	0	0.00	0	0.00
PgR								
Positive	79	69.91	248	74.70	68	71.58	68	71.58
Negative	34	30.09	84	25.30	27	28.42	27	28.42
Radiotherapy								
Yes	6	5.31	9	2.71	1	1.05	1	1.05
No	107	94.69	323	97.29	94	98.95	94	98.95

ILC, invasive lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor

that adjuvant CT was not associated with improved OS in patients with stage I/II luminal ILC. However, they did not mention lymph node metastasis, and it is difficult to assess the difference in results between our study and their studies. Nonneville et al. [25] also evaluated whether perioperative CT improved the prognosis of luminal ILC. They compared the prognosis of DFS and OS between endocrine therapy alone and endocrine therapy with CT and showed that CT improved the prognosis. Additionally, their subgroup analysis showed that CT did not significantly improve the prognosis in low-risk patients based on their original scoring system. However, high-risk patients could derive significant benefits from CT. Their findings and ours are similar because CT is effective in more advanced cases. However, our analysis was limited due to the small number of cases, and we could not draw definitive conclusions. Trapani et al. recently conducted a meta-analysis of eight retrospective studies on ILC, including all subtypes, and reported that CT does not contribute to an improvement in OS [26]. It is necessary to conduct similar large-scale studies for each subtype. Recently, the use of Oncotype Dx (Genomic Health, Redwood City, California), which provides the recurrence score (RS) and chemosensitivity in luminal breast cancer, is becoming more widespread. However, the utility of Oncotype Dx in ILC remains controversial [27]. For example, it has been reported that histological grade affects RS and that ILC rarely shows high RS [19, 28]. Kizy et al. [29] reported that adjuvant CT did not improve the prognosis of ILC in the intermediate and high RS groups. In contrast, Weiser et al. [19] found that the high RS group in ILC, particularly those with N1, obtained a longer prognosis by performing CT. Our findings are consistent with their results because the N1 group benefitted more from CT. As more data accumulate on the use of OncotypeDx for ILC, the indications for CT for ILC might become clearer.

Our study had some limitations. First, central review of the samples was not performed in the NCD. There are studies that report that approximately 60% of tumors diagnosed as ILC by local pathology are confirmed to be ILC by central pathology [30, 31]. Considering the challenges of pathological diagnosis in ILC, central review of the samples may be necessary. Second, NCD lacked information regarding Ki-67; therefore, we could not classify the luminal subtypes, luminal A and B. Luminal B usually has a poorer prognosis than A; however, we could not compare the prognosis between the ILC and IDC in the luminal A

Table 4 Patient characteristics of the matched cohort for examination of the effects of chemotherapy in pT1-2N1 luminal ILC

	Pre matching				Post matching			
	Chemotherapy		No-chemotherapy		Chemotherapy		No-chemotherapy	
	n	%	n	%	n	%	n	%
Total	185		130		83		83	
Age (years)								
< 20	0	0.00	0	0.00	0	0.00	0	0.00
20–29	0	0.00	0	0.00	0	0.00	0	0.00
30–39	6	3.24	2	1.54	2	2.41	2	2.41
40–49	78	42.16	29	22.31	28	33.73	28	33.73
50–59	57	30.81	26	20.00	24	28.92	24	28.92
60–69	36	19.46	26	20.00	21	25.30	21	25.30
70–79	8	4.32	29	22.31	8	9.64	8	9.64
≥ 80	0	0.00	18	13.85	0	0.00	0	0.00
Menopause status								
Menopause	84	45.41	92	70.77	46	55.42	46	55.42
Premenopause	101	54.59	38	29.23	37	44.58	37	44.58
Tumor size								
< 2 cm	40	21.62	32	24.62	20	24.10	20	24.10
≥ 2 cm	145	78.38	98	75.38	63	75.90	63	75.90
ER								
Positive	185	100.00	130	100.00	83	100.00	83	100.00
Negative	0	0.00	0	0.00	0	0.00	0	0.00
PR								
Positive	152	82.16	105	80.77	72	86.75	72	86.75
Negative	33	17.84	25	19.23	11	13.25	11	13.25
Radiotherapy								
Yes	13	7.03	8	6.15	4	4.82	4	4.82
No	172	92.97	122	93.85	79	95.18	79	95.18

ILC, invasive lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor

and B groups separately. Third, information about the histological grade was lacking in the NCD. The histological grade is strongly correlated with the prognosis of breast cancer [32]. ILC has a higher proportion of low to intermediate histological grade compared to IDC [33]. Therefore, differences in the prognosis of ILC and IDC may be more significant than the results of this study when adjusting for histological grade as a variable. Fourth, NCD lacked information regarding histological variants in ILC, such as classical, solid, alveolar, mixed non-classical, and trabecular variants. Although it has been shown that solid and mixed non-classical variants are more closely related to poor prognosis [3], how these variants affect prognostic comparison by subtypes is unclear. Furthermore, classical ILC is often the luminal type, and it has been reported to exhibit variable response to CT [26]. However, this study did not investigate how these subtypes influence the effectiveness of CT.

Lastly, the lack of data on activities of daily living, such as the Eastern Cooperative Oncology Group Performance Status, might have affected the results [34]. Notably, the prognostic comparison between the ET + CT and ET-only groups at pT1-2N1 showed a significant difference in OS compared with DFS. This might be because the ET-only group included more patients who could not receive CT due to comorbidities or poor performance status. Finally, it is necessary to accumulate data because the number of patients was small in the luminal HER2, HER, and TN groups. Therefore, the study of ILC requires continuous effort and the accumulation of data at multiple institutions.

Conclusion

Luminal ILC had a poorer prognosis than luminal IDC, which contributed to the worse prognosis of ILC than that of IDC. Different therapeutic approaches from luminal IDC are essential for a better prognosis of luminal ILC.

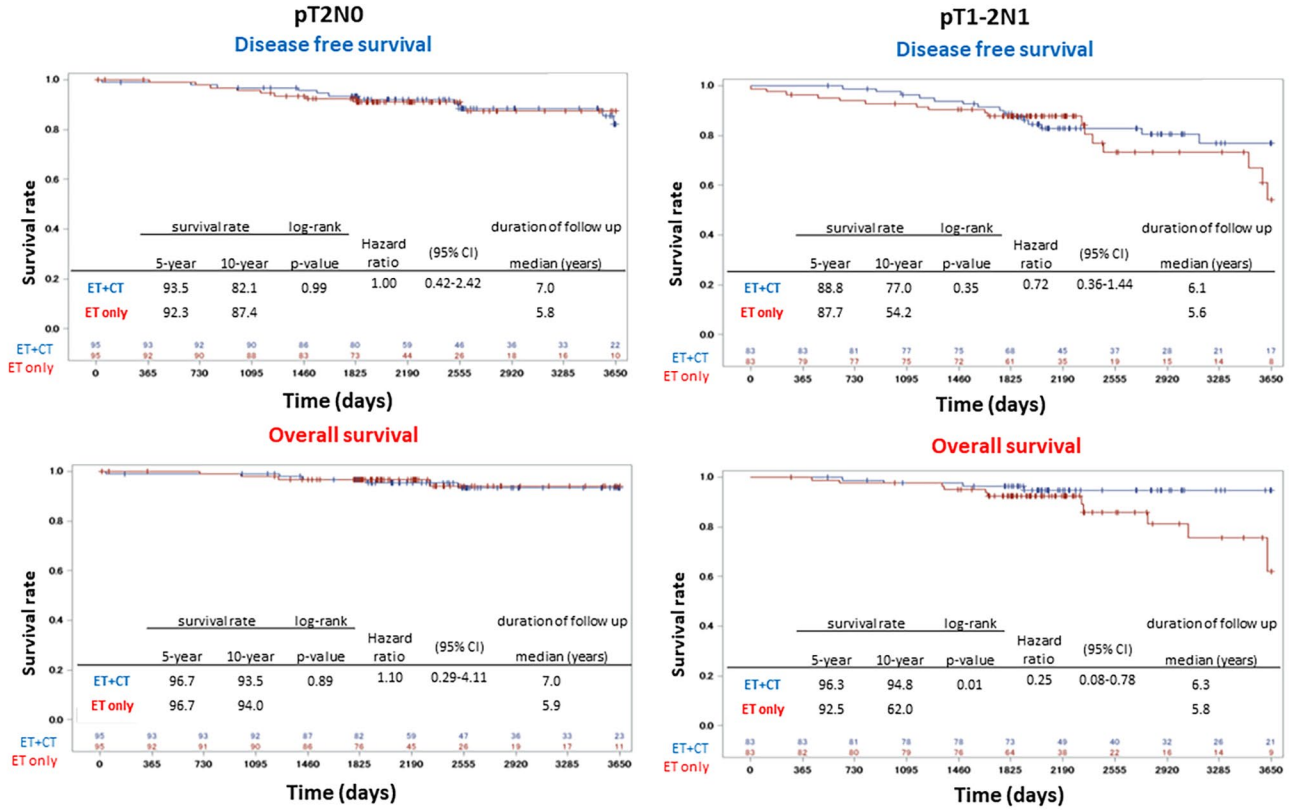

Fig. 5 Prognosis of ET + CT group and ET-only group in luminal ILC. ILC, invasive lobular carcinoma; ET, endocrine therapy; CT, chemotherapy

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Data availability The datasets generated during and/or analyzed during the current study are not publicly available due to ethical restrictions but are available from the corresponding author on reasonable request.

Declarations

Competing interests HK reports received consultation fees from Mitsubishi-Tanabe Pharma Corporation and EPS Corporation and speaker fees from Chugai Pharmaceutical Co., Ltd. and Johnson and Johnson KK. HK and NK are affiliated with the Department of Health Quality Assessment at the University of Tokyo, a social collaboration department supported by the National Clinical Database, Johnson and Johnson K.K., Nipro Corporation, and Intuitive Surgical Sàrl. NN received honoraria from Astra Zeneca, Chugai, Daiichi Sankyo, Pfizer, Eli Lilly and MSD; and research funding from Chugai, Daiichi Sankyo, Pfizer, Eisai, Mochida and Novartis. SS received honoraria from Astra Zeneca, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, Kyowa Kirin, MSD, Ono, Pfizer, Taiho and Takeda; and research funding from Astra Zeneca, Chugai, Daiichi Sankyo, MSD and Taiho. MT reports received honoraria from Chugai, Takeda, Pfizer, Kyowa-Kirin, Taiho, Eisai, Daiichi-Sankyo, AstraZeneca, Eli Lilly and companies, MSD, Exact Science, Novartis, Shimadzu, Yakult, Nippon Kayaku, Devicore Medical Japan, and Sysmex; and research funding from Chugai, Takeda, Pfizer, Taiho, JBCRG assoc., KBCRN assoc., Eisai, Eli Lilly, Daiichi-Sankyo, AstraZeneca, Astellas, Shimadzu, Yakult, Nippon Kayaku, AFI technology, Luxonus, Shionogi, GL Science, and Sanwa Shurui. YA, SA, NK, YS, HJ, and MT have no relevant financial or non-financial interests to disclose.

Ethics approval This study was performed in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Aichi Cancer Center (5.8.2019/No.2019-1-042).

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