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CLINICAL TRIAL

Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma

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Abstract Invasive lobular carcinomas (ILC) show better clinical behaviour compared with other histological types, but significantly lower pathological complete response (pCR) rates after neoadjuvant chemotherapy (NACT). We investigated whether factors influencing pCR rate in ILC after NACT can be identified and whether clinical outcome is different. 9,020 breast cancer patients from nine German neoadjuvant trials with known histological type were pooled. 11.7 % of tumours were ILC. Endpoints were: pCR rate, surgery type and survival. ILC was associated with older age, larger tumour size, lymph node negativity, lower grade and positive hormone-receptor-status (HR). Patients with ILC achieved a significantly lower pCR rate compared with non-ILC patients (6.2 vs. 17.4 %, $P < 0.001$). The pCR rate was 4.2 % in ILC/HR+/G1-2, 7.0 % in ILC with either HR− or G3, and 17.8 % in ILC/HR−/G3. Mastectomy rate was higher in ILC compared with non-ILC patients irrespective of response to NACT (pCR: 27.4 vs. 16.6 %, $P = 0.037$ and non-pCR: 41.8 % vs. 31.5 %, $P < 0.0001$). Age and HR independently predicted pCR in ILC. In ILC patients, pCR did not predict distant disease free (DDFS) and loco-regional disease free survival (LRFS), but overall survival (OS). Non-pCR patients with ILC had significantly better DDFS ($P = 0.018$), LRFS ($P < 0.0001$) and OS ($P = 0.044$) compared with non-ILC patients. Patients with ILC had a low chance of obtaining a

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pCR and this is not well correlated with further outcome. The mastectomy rate was considerably high in ILC patients even after obtaining a pCR. We, therefore, suggest to offer NACT mainly to ILC patients with HR-negative tumours.

Keywords Breast cancer · Invasive lobular carcinoma · Non-lobular carcinoma · Pathological complete response · Neoadjuvant chemotherapy · Survival

Introduction

With an incidence of 5–15 %, invasive lobular carcinoma (ILC) represents the second most common histological type of breast cancer, with distinct clinical, biological and molecular features compared with non-lobular carcinoma (non-ILC) [1, 2]. In comparison with non-ILC, ILC is significantly more likely to occur in older patients, to be of larger size, hormone-receptor positive, of intermediate grade and without vascular invasion [3, 4]. Pleomorphic lobular carcinomas of the breast display histological features associated with ILC, yet they also exhibit more nuclear atypia and pleomorphism, and an aggressive clinical behaviour [5–7].

The pathological complete response (pCR) rate after neoadjuvant chemotherapy (NACT) seems to be significantly lower in patients with ILC [8, 9]. The overall clinical behaviour, however, seems to be better for ILC than for other histological types [10]. There is still controversy as to whether the prognosis of lobular carcinomas differs from ductal invasive carcinomas [5].

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The primary aim of our individual patient data-based pooled analysis was to analyse the response to NACT in patients with ILC compared to non-ILC. The secondary aims of this analysis were to assess the predictive value of pCR on surgery and outcome in this subset.

Patients and methods

Between 1998 and 2010, 9,197 breast cancer patients were enrolled in nine prospectively randomized multicentre, neoadjuvant trials in Germany, all having comparable main eligibility criteria [9, 11, 12].

A prospectively collected database of patients receiving an anthracycline-taxane-based NACT for breast cancer was established. Clinical response was determined based on changes in tumour size seen in radiographic assessment (mainly ultrasound) and clinical examination. Histological type, tumour grade, and oestrogen-, progesterone- and HER2-receptor status were determined locally and/or centrally on pre-treatment core-biopsies. Local histology has been substituted by central histology, whenever available. Mixed histologies were rated as non-ILC. Positive hormone-receptor (HR) status was defined as $\geq$10 % of cells stained positive for oestrogen (ER) and/or progesterone receptor (PgR), HER2-receptor was positive if either local or central immunohistochemical staining was 3+ or fluorescent in situ hybridization was amplified (ratio of HER2/CEP17 $>$ 2.2) [13]. Central assessment was used whenever available. Chemotherapy details of the individual trials are given in Supplementary Table S1. In the TECHNO, GeparQuattro and GeparQuinto trial, all patients with HER2+ disease received neoadjuvant and adjuvant lapatinib or trastuzumab [14, 15]. In the GeparQuinto trial, patients in the HER2-negative setting were randomized to chemotherapy with or without bevacizumab [16]. In the Gepardo (no follow-up data) and Geparduo trial all patients received pre-surgical tamoxifen [9, 17]. Adjuvant endocrine treatment was administered to all HR-positive patients and postsurgical radiotherapy was given according to effective guidelines [18]. Data on radiotherapy have been captured in the GeparTrio, GeparQuattro and GeparQuinto studies. These three studies with 6,135 patients represent 68 % of the whole analysis set. Data on radiotherapy are available from 3,143 of these 6,135 patients representing 51 % of the available patients and 36 % of the total study population. Pathological complete response (pCR) was defined as no invasive and no non-invasive residual disease in breast and lymph nodes (ypT0 ypN0). Distant disease free survival (DDFS) was defined as time from randomization to any distant relapse or death irrespective of cause. Loco-regional disease free survival (LRFS) was defined as time from randomization to breast, chest wall recurrence or regional lymph node

recurrences irrespective of distant recurrences. Overall survival (OS) was defined as time from randomization to death irrespective of cause.

Statistical analysis

Statistical analyses were performed using SPSS v21.0 and SAS v9.2. Age (<35; 35 to <40; 40 to <45; 45 to <50; 50 to <60; ≥60 years); clinical tumour stage [cT1-3 vs. cT4 (locally advanced)], clinical nodal status (cN0 negative vs. cN1 positive), (1 or 2 vs. 3); HR-status (positive vs. negative), HER2 treatment (HER2-negative; HER2-positive without and HER2-positive with anti-HER2 treatment) HER2/HR biological subtype (HR-positive/HER2-negative/G1-2; HR-positive/HER2-negative/G3; HER2-positive/HR-positive, HER2-positive/HR-negative, triple-negative) and study were used in the multivariable models. Endpoints of the analyses were: pCR, surgery type, DDFS, LRFS and OS. Differences in patient characteristics in the ILC and non-ILC group were analysed using χ^2 tests. Two-sided P value ≤ 0.05 was considered to be statistically significant. Univariable and multivariable logistic regression models were performed to estimate the prediction of pCR by clinical factors. The odds ratio (OR) and corresponding 95 % CI are given. DDFS, LRFS and OS were calculated using the Kaplan–Meier method and the log-rank test. Prognostic factors for survival in ILC were tested for statistical significance using a multivariable Cox proportional hazards model with Firth's correction for monotone likelihood to account for the low events/pCRs. Hazard ratios and the corresponding 95 % CI are given. All multivariable models were adjusted for studies, with significance level set to 0.05. No correction for multiple testing was performed.

Results

Patient baseline characteristics

In this pooled analysis, information on histological type was available in 9,020 of the 9,197 primary breast cancer patients (98.1 %). ILC was diagnosed in 1,051 (11.7 %) and non-ILC in 7,969 patients (7,282 invasive ductal carcinoma and 687 not otherwise specified). Central histology was performed in 1,411 cases. In this cohort, the number of ILCs was 157 (11.1 %), compared to 195 (13.8 %) by local assessment (concordance rate 89 %, kappa 0.51).

Patients with ILC were significantly older, had larger tumours, but less lymph node involvement at baseline. Overall 1,092 patients presented with locally advanced disease [cT4a-c and inflammatory breast cancer (cT4d)]; 124 (11.8 %) in the ILC group versus 968 (12.2 %) in the non-ILC group ($P = 0.728$). ILC tumours were significantly more often grade 1 and 2, HR-positive and HER2-negative ($P < 0.001$). Only 8.6 % of the ILC tumours were triple-negative breast cancers compared with 25.7 % in the non-ILC group ($P < 0.0001$) (Table 1).

Pathological complete response analysis

Sixty-five of 1,051 patients with ILC had a pCR (6.2 %) compared to 1,384 of 7,969 patients with non-ILC (17.4 %; $P < 0.001$). In the ILC group, younger age, higher grade, HR-negative status and also subtype were significantly associated with higher pCR rates in univariable analysis (Table 2). ILC of low and intermediate grade and positive HR-status (ILC/HR+/G1-2) had a pCR rate of 4.2 % compared to 7.0 % in ILC either HR− or G3 ($P = 0.36$) and 17.8 % in ILC HR− and high grade ($P = 0.004$). In patients of 50 years and older, the pCR rate did not differ between G3/HR- and G1-2/HR+ (4.2 vs. 3.7 %). However, there was a significant difference in pCR between these two groups in the age cohorts <40 years (37.5 vs. 9.8 %; $P = 0.033$) and 40–50 years (30.8 vs. 3.9 %; $P < 0.0001$). In multivariable analysis age, HR-status and subtype, all independently predicted pCR in the ILC group (Table 3).

HER2 status was known in 7,095 patients. HER2 was positive in 102/767 ILC (13.3 %) and in 1,828/6,328 non-ILC (28.8 %). Six of the 62 HER2-positive ILC patients (9.7 %) not receiving anti-HER2 treatment and eight of the 40 HER2-positive patients with ILC (20 %) receiving anti-HER2 treatment showed a pCR ($P = 0.003$) (Tables 2, 3).

Surgery and radiotherapy

The rate of breast conserving surgery (BCS) was lower in the ILC group with 59.1 % (585 of 994) versus 71.1 % (5,431 of 7,634) in non-ILC ($P < 0.0001$). Patients with pCR were less likely to receive BCS in the ILC group compared to the non-ILC group (72.6 vs. 83.4 %, $P = 0.037$). In the non-pCR group mastectomy (primary or secondary) was performed more frequently for ILC, than for non-ILC (41.8 vs. 31.5 %, $P < 0.0001$) (Fig. 1). Histology remained an independent predictor for mastectomy (OR 1.76 [95 % CI 1.47–2.09] $P < 0.0001$) in multivariable analysis after adjusting for age, tumour stage and nodal involvement, grading, HR-status, HER2-status, pCR and study. In the ILC group, after adjusting for the aforementioned baseline factors only T4 (OR 3.74 [95 % CI 2.25–6.22] $P < 0.0001$) and nodal involvement (OR 1.56 [95 % CI 1.13–2.15] $P = 0.007$) independently predicted a mastectomy. In the non-ILC group, in addition to tumour stage and nodal involvement, pCR, age, and HER2-status predicted independently the odds for mastectomy (data not shown).

Table 1 Baseline characteristics at start of neoadjuvant therapy

Characteristics at baseline	All patients ($N = 9{,}020$)		Patients ILC ($N = 1{,}051$)		Patients non-ILC ($N = 7{,}969$)		*P*-value
	N	Valid %	*N*	Valid %	*N*	Valid %	
Age							<0.0001
<35	575	6.4	26	2.5	549	6.9	
35–39.99	894	9.9	61	5.8	833	10.5	
40–44.99	1,417	15.7	136	12.9	1,281	16.1	
45–49.99	1,669	18.5	201	19.1	1,468	18.4	
50–59.9	2,679	29.7	362	34.4	2,317	29.1	
≥60	1,786	19.8	265	25.2	1,521	19.1	
Tumour stage							<0.001
cT1	622	6.9	48	4.6	574	7.3	
cT2	5,743	64.1	605	57.8	5,138	64.1	
cT3	1,505	16.8	269	25.7	1,236	15.6	
cT4a-c	604	6.7	82	7.8	522	6.6	
cT4d	488	5.4	42	4.0	446	5.6	
Missing	58		5		53		
Nodal status							0.001
cN0	4,349	48.8	541	52.3	3,808	48.4	
cN1	4,049	45.8	444	42.9	3,635	46.2	
cN2	370	4.2	32	3.1	338	4.3	
cN3	110	1.2	17	1.6	93	1.2	
Missing	112		17		95		
Tumour Grade							<0.0001
1	328	3.8	49	5.0	279	3.6	
2	4,754	54.7	738	75.2	4,016	52.1	
3	3,614	41.6	195	19.9	3,419	44.3	
Missing	324		69		255		
Hormone-receptor status							<0.0001
Negative	2,975	33.9	118	11.5	2,857	36.9	
Positive	5,791	66.1	904	88.5	4,887	63.1	
Missing	254		29		225		
HER2 status							<0.0001
Negative	5,172	72.9	665	86.7	4,507	71.2	
Positive	1,923	27.1	102	13.3	1,821	28.8	
Missing	1,641		284		1,925		
HER2 treatment							<0.0001
HER2 negative	5,172	72.9	665	86.7	4,507	71.2	
HER2 positive w/o	709	10.0	62	8.7	647	10.2	
HER2 positive with	1,214	17.1	40	5.2	1,174	18.6	
Subtype							<0.0001
HR+/HER2−/G1-2	2,481	35.9	497	68.1	1,984	32.1	
HR+/HER2−/G3	891	12.9	70	9.6	821	13.3	
HR+/HER2+	1,076	15.6	77	10.5	999	16.2	
HR−/HER2+	805	11.7	23	3.2	782	12.7	
Triple-negative	1,650	23.9	63	8.6	1,587	25.7	
Missing	2,117		321		1,796		

ILC invasive lobular carcinoma

Table 2 pCR rate in ILC and non-ILC overall and in subgroups

	pCR rate		Univariate analysis pCR for ILC ($N = 1{,}051$)				pCR rate		Univariate analysis pCR for non-ILC ($N = 7{,}969$)			
	N	%	OR	95 % CI for OR		Sig.	*N*	%	OR	95 % CI for OR		Sig.
				Lower	Upper					Lower	Upper	
Total	65	6.2					1,384	17.4				
Age												
≥60	10	3.8	1.00			<0.001	221	14.5	1.00			<0.001
≥50 to <60	18	5.0	1.33	0.61	2.94	0.474	362	15.6	1.44	1.21	1.72	0.356
≥45 to <50	7	3.5	0.92	0.34	2.46	0.868	263	17.9	1.28	1.06	1.56	0.012
≥40 to <45	15	11.0	3.16	1.38	7.24	0.006	249	19.4	1.42	1.16	1.73	0.001
≥35 to <40	7	11.5	3.31	1.20	9.07	0.020	152	18.2	1.31	1.05	1.65	0.018
<35	8	30.8	11.33	3.98	32.24	<0.001	137	25.0	1.96	1.54	2.49	<0.001
Tumour stage												
T4	12	9.7	1.00			0.093	120	12.4	1.00			<0.001
T1-3	53	5.7	0.57	0.30	1.10		1,257	18.1	1.56	1.28	1.91	
Nodal status												
N+	32	6.5	1.00			0.701	648	15.9	1.00			<0.001
N0	32	5.9	0.91	0.55	1.50		726	19.1	1.24	1.11	1.40	
Grading												
G1-2	41	5.2	1.00			0.037	473	11.0	1.00			<0.001
G3	18	9.2	1.85	1.04	3.30		836	24.5	2.62	2.31	2.96	
Hormone-receptor status												
Positive	41	4.5	1.00			<0.001	471	9.6	1.00			<0.001
Negative	17	14.4	3.54	1.94	6.47		852	29.8	3.98	3.52	4.51	
HER2 status												
HER2−	41	6.2	1.00			0.905	757	16.8	1.00			<0.001
HER2+	14	13.7	1.60	1.40	1.82		444	24.4	1.60	1.40	1.82	
HER2 status anti-HER2 treatment												
HER2−	41	6.2	1.00			0.006	757	16.8	1.00			<0.001
HER2+w/o	6	9.7	1.63	0.66	4.01	0.287	115	17.8	1.07	0.86	1.33	0.535
HER2+w	8	20.0	3.80	1.65	8.78	0.002	329	28.0	1.93	1.66	2.24	<0.001
Subtype												
HR+/Her2−/G1-2	23	4.6	1.00			<0.001	111	5.6	1.00			<0.001
HR+/HER2-/G3	2	2.9	0.61	0.14	2.63	0.504	109	13.3	2.58	1.96	3.41	<0.001
HER2+/HR+	7	9.1	2.06	0.85	4.98	0.108	188	18.8	3.91	3.05	5.02	<0.001
HER2+/HR−	5	21.7	5.72	1.95	16.78	0.001	247	31.6	7.79	6.11	9.94	<0.001
TNBC	11	17.5	4.36	2.01	9.45	<0.001	511	32.2	8.01	6.44	9.97	<0.001

CI confidence interval, *ILC* invasive lobular carcinoma, *OR* odds ratio, *pCR* pathological complete response

Overall, 76.6 % of the patients treated by mastectomy (25.8 % radiotherapy (RT) to the chest wall, 2.5 % to the lymph nodes (LN) and 48.3 % to the chest wall and LN) and 95.7 % of the patients treated with BCS received adjuvant RT (62.3 % to the breast, 0.1 % to the LN and 33.3 % to breast and LN). There was no difference in the use of RT between patients with ILC and non-ILC (mastectomy $P = 0.0746$; BCS $P = 0.161$).

Survival analysis

During a median follow-up of 53.8 months (range 0–117 months), 1,554 distant relapses (17.7 %; 178 ILC and 1,376 non-ILC), 597 loco-regional relapses (6.8 %; 43 ILC and 554 non-ILC) and 1,159 deaths (13.2 %; 132 ILC and 1,027 non-ILC) were observed. Overall DDFS and OS were not different between ILC and non-ILC (HR 1.08

Table 3 Multivariable Analysis for pCR for the whole population and according to histological subtype

	Overall multivariable analysis for pCR				Multivariable analysis pCR for ILC				Multivariable analysis for non-ILC			
	OR	95 % CI for OR		Sig.	OR	95 % CI for OR		Sig.	OR	95 % CI for OR		Sig.
		Lower	Upper			Lower	Upper			Lower	Upper	
Age												
≥60	1.00			0.001	1.00			0.046	1.00			0.004
≥50 to <60	1.17	0.95	1.45	0.145	1.71	0.66	4.45	0.270	1.15	0.93	1.44	0.198
≥45 to <50	1.37	1.09	1.72	0.006	1.25	0.39	3.97	0.711	1.38	1.09	1.74	0.007
≥40 to <45	1.49	1.18	1.88	0.001	2.40	0.78	7.44	0.129	1.47	1.16	1.87	0.001
≥35 to <40	1.40	1.08	1.83	0.012	4.16	1.21	14.26	0.023	1.34	1.02	1.76	0.033
<35	1.68	1.26	2.25	<0.001	10.00	1.89	52.87	0.007	1.61	1.20	2.16	0.002
Tumour stage												
T4	1.00			<0.001	1.00			0.448	1.00			<0.001
T1-3	1.57	1.25	1.97		0.71	0.29	1.72		1.64	1.30	2.08	
Nodal status												
N+	1.00			0.006	1.00			0.469	1.00			0.003
N0	1.21	1.06	1.39		0.78	0.40	1.53		1.24	1.07	1.42	
Histology												
Lobular	1.00			<0.001								
Non-lobular	1.81	1.31	2.52									
Grading												
G1-2	1.00			<0.001	1.00			0.955	1.00			<0.001
G3	1.74	1.51	2.00		1.02	0.44	2.39		1.77	1.53	2.05	
Hormone-receptor status												
Positive	1.00			<0.001	1.00			0.002	1.00			<0.001
Negative	3.26	2.83	3.77		3.53	1.57	7.91		3.25	2.81	3.76	
HER2 status												
HER2−	1.00			<0.001	1.00			0.114	1.00			<0.001
HER2+	1.65	1.42	1.91		2.05	0.84	4.99		1.65	1.42	1.92	
HER2 status treatment												
HER2+with Tx	1.00			<0.001	1.00			0.102	1.00			<0.001
HER2+w/o Tx	0.51	0.37	0.70	<0.001	0.28	0.04	1.99	0.204	0.50	0.36	0.70	<0.001
HER2−	0.49	0.41	0.58	<0.001	0.31	0.11	0.91	0.033	0.48	0.40	0.58	<0.001
Subtype												
HR+/Her2−. G1-2	1.00			<0.001	1.00			0.001	1.00			<0.001
HR+/HER2-/G3	2.40	1.84	3.14	<0.001	0.60	0.14	2.69	0.509	2.63	1.99	3.48	<0.001
HER2+/HR+	3.68	2.90	4.67	<0.001	1.70	0.62	4.66	0.304	3.96	3.08	5.10	<0.001
HER2+/HR−	7.91	6.23	10.06	<0.001	6.10	1.78	20.85	0.004	8.42	6.55	10.82	<0.001
TNBC	7.26	5.90	8.93	<0.001	4.01	1.74	9.21	0.001	7.72	6.20	9.62	<0.001

CI confidence interval, *ILC* invasive lobular carcinoma, *OR* odds ratio, *pCR* pathological complete response

[95 % CI 0.92–1.26] log-rank $P = 0.349$ and HR 1.09 [95 % CI 0.91–1.31] log-rank $P = 0.351$, respectively). However, patients with ILC had a significantly better LRFS compared to non-ILC (HR 1.80 [95 % CI 1.32–2.45] log-rank $P < 0.001$). There was no significant difference in DDFS, LRFS and OS in the ILC group for pCR patients compared to non-pCR patients (HR 1.06 [95 % CI 0.56–2.01] log-rank $P = 0.850$ and HR 0.83 [95 % CI 0.26–2.67] log-rank $P = 0.749$ and HR 1.59 [95 % CI 0.65–3.90] log-rank $P = 0.303$ respectively) (Fig. 2a–c). Patients achieving a pCR had a significantly worse DDFS with ILC than those with non-ILC (Fig. 2a). Histological type did not provide independent prognostic information for the pCR patients (HR 0.45; 95 % CI 0.19–1.099; $P = 0.08$) (Supplementary Table S2). In patients with a pCR LRFS and OS were similar between ILC and non-ILC

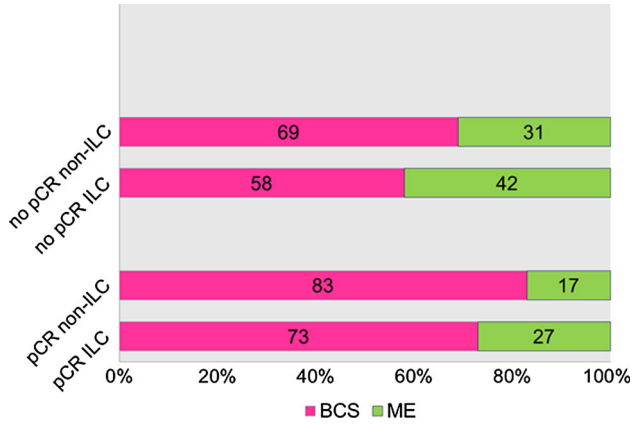

Fig. 1 Type of surgery according to pCR in ILC compared to non-ILC group. *BCS* breast conserving surgery, *ME* mastectomy

(Fig. 2b–c). However, non-pCR patients with ILC achieved a significantly better DDFS (HR 1.22 [95 % CI 1.03–1.43] log-rank $P = 0.018$), LRFS (HR 2.05 [95 % CI 1.49–2.83] log-rank $P < 0.0001$) and OS (HR 1.21 [95 % CI 1.02–1.46] log-rank $P = 0.044$) compared with non-ILC. In the ILC group, pCR and age were independent prognostic factors only for OS (Table 4).

Discussion

In general, neoadjuvant chemotherapy for primary breast cancer is used irrespective of the histopathological type. Using data from 1,051 patients with ILC in this pooled analysis, it was shown that this cohort had a significantly lower pCR rate compared with non-ILC patients. However, biologically aggressive ILCs (HR− and G3) especially in younger patients achieved a pCR rate comparable to non-ILCs [8, 10, 19, 20].

Patients with lobular carcinomas were significantly more likely to receive a mastectomy even if a pCR was obtained after neoadjuvant chemotherapy [21–23]. One reason to use neoadjuvant chemotherapy is usually clinical down-staging for better operability. The mean tumour size in our cohort was 47 mm in ILC and 43 mm in the non-ILC group and more patients in the ILC group had a cT3 or locally advanced tumour (T4a–d) (37.5 vs. 27.8 %) at baseline, which supports this hypothesis. This analysis cannot explain why patients with a good response to neoadjuvant chemotherapy were still treated with a mastectomy instead of breast conserving surgery. We have no further information on surgical margins, however, the general prerequisite for breast conserving surgery is tumour free margins. According to the study protocols, pre-surgical imaging was performed using breast ultrasound and mammography. Data on the use of MRI were not captured.

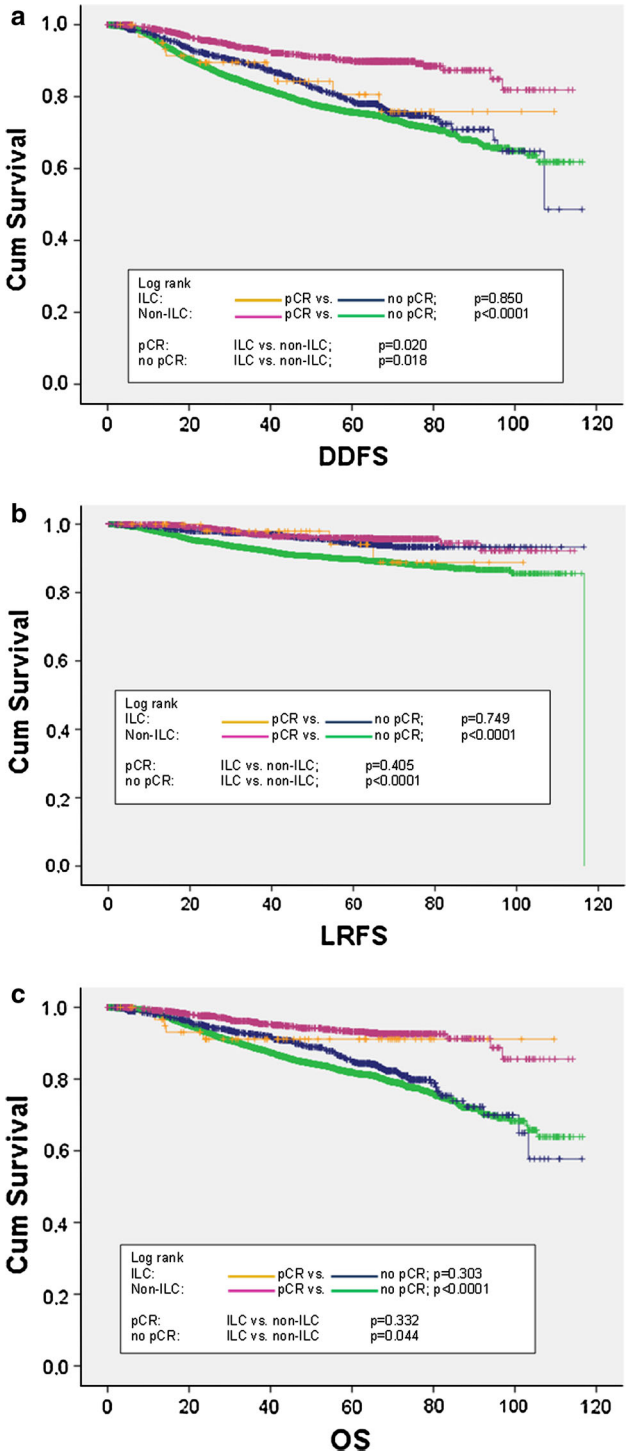

Fig. 2 Distant Disease free (DDFS) (**a**) local recurrence free (LRFS) (**b**) and overall survival (OS) (**c**) according to histological type and pCR

It is difficult to determine the exact extent of residual ILC lesions by imaging which may explain the higher mastectomy rate in ILC patients. It has not conclusively been proven that the local control or survival is better with more

Table 4 Multivariable analysis for DDFS, LRFS, OS in the group with invasive lobular carcinoma

	Multivariable analysis for DDFS in ILC patients				Multivariable analysis for LRFS in ILC				Multivariable analysis for OS in ILC			
	HR	95 % CI for HR		Sig.	HR	95 % CI for HR		Sig.	HR	95 % CI for HR		Sig.
		Lower	Upper			Lower	Upper			Lower	Upper	
Age												
≥60	1.00			0.154	1.00			0.212	1.00			0.045
≥50 to <60	0.75	0.44	1.28	0.288	1.20	0.35	4.18	0.774	0.55	0.29	1.06	0.073
≥45 to <50	0.88	0.49	1.58	0.666	1.96	0.56	6.85	0.291	0.69	0.34	1.41	0.311
≥40 to <45	1.32	0.73	2.38	0.365	2.63	0.68	10.17	0.161	1.13	0.57	2.27	0.723
≥35 to <40	1.77	0.85	3.70	0.128	5.44	1.32	22.44	0.019	1.98	0.90	4.35	0.089
<35	1.67	0.51	5.53	0.398	0.78	0.03	19.67	0.879	1.27	0.31	5.19	0.737
Tumour stage												
T4	1.00			<0.001	1.00			0.075	1.00			0.005
T1-3	0.43	0.27	0.68		0.38	0.13	1.10		0.45	0.26	0.78	
Nodal Status												
N+	1.00			<0.001	1.00			0.691	1.00			<0.001
N0	0.33	0.21	0.51		0.84	0.36	1.97		0.34	0.20	0.59	
Grading												
G1-2	1.00			0.041	1.00			0.001	1.00			0.020
G3	1.65	1.02	2.65		4.30	1.80	10.31		1.94	1.11	3.37	
Hormone-receptor status												
Negative	1.00			<0.001	1.00			0.001	1.00			<0.001
Positive	0.22	0.13	0.36		0.18	0.07	0.47		0.17	0.09	0.29	
HER2 status												
HER2−	1.00			0.256	1.00			0.283	1.00			0.470
HER2+with	0.43	0.11	1.61	0.209	0.31	0.01	7.50	0.475	0.66	0.17	2.51	0.541
HER2+w/o	0.68	0.33	1.39	0.290	0.27	0.05	1.65	0.158	0.64	0.28	1.47	0.293
pCR												
Yes	1.00			0.075	1.00			0.214	1.00			0.009
No	2.20	0.93	5.23		2.78	0.55	13.99		6.12	1.56	24.02	
Surgery type					1.00			0.891				
Mastectomy												
BCS					0.94	0.39	2.24					

CI confidence interval, *DDFS* distant disease free survival, *HR* hazard ratio, *ILC* invasive lobular carcinoma, *LRFS* loco-regional disease free survival, *OS* overall survival, *pCR* pathological complete response

radical surgery [24]. On the other hand, we found a significantly better LRFS for ILC compared to non-ILC. But type of surgery was not an independent prognostic factor for LRFS. The rate of postmastectomy radiotherapy was high (77 %) and similar in ILC and non-ILC patients. A generally higher radiosensitivity for ILC has been reported [25, 26].

There is still controversy whether the prognosis of ILC differs from non-ILC [5, 27–29]. Contrary to other authors, we observed better DDFS and OS for ILC compared to non-ILC [10]. Only pCR patients with ILC had a significantly worse distant disease free survival compared with non-ILC, which might be biased by heterogeneity of baseline factors. Non-pCR patients had a significantly better survival with ILC compared to non-ILC. Within the ILC group, none of the survival endpoints were different between pCR and non-pCR patients after neoadjuvant chemotherapy. pCR is a surrogate endpoint for predicting long-term clinical benefit on endpoints such as disease-free or overall survival [9, 30]. However, pCR seems especially important for tumours with more aggressive biological features.

Our pooled analysis has some strengths and limitations. To the best of our knowledge with more than 1,000 ILCs, this is the largest cohort of neoadjuvant treated lobular carcinomas to date. The number of pCRs in the ILC group

is considerably lower. To overcome this limitation, a Firth's correction for monotone likelihood was used for the Cox proportional model for the long-term outcome analyses. Lobular carcinomas included in neoadjuvant trials are naturally singled out since all eligible patients had to have some risks (e.g. large tumours) to be included into a neoadjuvant chemotherapy trial. Therapy changed over time, but all analyses had been adjusted for study. Moreover, all patients received an anthracycline-taxane based neoadjuvant backbone chemotherapy with or without anti-HER2 treatment. Data are based mainly on local pathology; however, central testing for HER2 was performed in 1,635 cases to reduce the rate of discrepant and missing HER2 cases [31, 32]. The rate of HER2-positive ILC is higher compared to data from the HERA trial [33]. In the older neoadjuvant trialsHER2-testing was not established as a routine method. This might explain the higher rate of HER2-positive cases compared to HERA [31]. In addition, we have performed central histology assessment in a subset of patients. In a study by Kiaer et al. the kappa value for ILC versus invasive ductal carcinoma between each central pathology and the country as a whole was 0.3 for a cohort of 379 breast carcinomas. Longacre et al. [34] showed in a cohort of $N = 35$ cases (including five lobular carcinomas) from a cancer registry that the accuracy for diagnosis of lobular carcinoma (comparing local assessment with reference pathology) had a mean of 90 % and a kappa value of 0.8. However, in their study, a prior training session was performed for the pathologists to standardize the evaluation, which was not done in our study. Our results are in line with the published data and show that the interobserver agreement for ILC is moderate [34, 35]. Hormone-receptor status and grade were used to further distinguish between more aggressive ILCs (i.e. pleomorphic ILC) because further details on histological characteristics have not been captured. The non-tubular architecture of ILC restricts the histological grade assessment in ILC, as most tumours will be grade 2. In a study by Rakha et al. [36] investigating 517 ILCs, 76 % of the ILCs were grade 2, while only 12 % were grade 1 or grade 3. Interestingly, grading was still an independent prognostic factor in that ILC cohort as well as in our analysis for DDFS, LRFS and OS. Genomic tests might add further information also in the cohort of ILCs as recently shown for the genomic grade index [37]. Anti-HER2 treatment works irrespective of histology [32]. Whether or not the outcome of ILC after neoadjuvant chemotherapy in patients with less aggressive features would have been the same as after endocrine therapy alone cannot be answered with this analysis since all patients received neoadjuvant chemotherapy [38].

In conclusion, patients with ILC had a very low chance of obtaining a pCR, and this did not predict for long-term outcome. The mastectomy rate was considerably higher in ILC patients even after obtaining a pCR. We, therefore, suggest that neoadjuvant chemotherapy should only be offered to ILC patients with hormone-receptor negative tumours. Whether patients with hormone-receptor positive tumours might be candidates for neoadjuvant endocrine therapy can only be answered by future studies.

Conflict of interest The authors have declared no conflicts of interest.

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