Breast Cancer Research and Treatment (2019) 175:379–387
https://doi.org/10.1007/s10549-019-05160-9

CLINICAL TRIAL

Adjuvant chemotherapy in lobular carcinoma of the breast: a clinicopathological score identifies high-risk patient with survival benefit

Alexandre de Nonneville[1] · Camille Jauffret[2] · Anthony Gonçalves[1] · Jean-Marc Classe[3] · Monique Cohen[2] · Fabien Reyal[4] · Chafika Mazouni[5] · Marie-Pierre Chauvet[6] · Nicolas Chopin[7] · Pierre-Emmanuel Colombo[8] · Eva Jouve[9] · Emile Darai[10] · Roman Rouzier[11] · Charles Coutant[12] · Pierre Gimbergues[13] · Anne-Sophie Azuar[14] · Christine Tunon de Lara[15] · Eric Lambaudie[2] · Gilles Houvenaeghel[2]

Received: 11 June 2018 / Accepted: 5 February 2019 / Published online: 13 February 2019

Abstract

Background Invasive lobular carcinomas (ILCs) represent approximately 10% of all breast cancers. Despite this high frequency, benefit of adjuvant chemotherapy (CT) is still unclear.

Methods Our objective was to investigate the impact of CT on survival in ILC. Patients were retrospectively identified from a cohort of 23,319 patients who underwent primary surgery in 15 French centers between 1990 and 2014. Only ILC, hormone-positive, human epidermal growth factor 2 (HER2)-negative patients who received adjuvant endocrine therapy (ET) were included. End-points were disease-free survival (DFS) and overall survival (OS). A propensity score for receiving CT, aiming to compensate for baseline characteristics, was used.

Results Of a total of 2318 patients with ILC, 1485 patients (64%) received ET alone and 823 (36%) received ET + CT. We observed a beneficial effect of addition of CT to ET on DFS and OS in multivariate Cox model (HR = 0.61, 95% confidence interval, CI [0.41–0.90]; $p = 0.01$ and 0.52, 95% CI [0.31–0.87]; $p = 0.01$, respectively). This effect was even more pronounced when propensity score matching was used. Regarding subgroup analysis, low-risk patients without CT did not have significant differences in DFS or OS compared to low-risk patients with CT.

Conclusion ILC patients could derive significant DFS and OS benefits from CT, especially for high-risk patients.

Keywords Adjuvant chemotherapy · Breast cancer · Lobular · Hormone receptor-positive

Abbreviations

CI	Confidence interval
CT	Adjuvant chemotherapy
DFS	Disease-free survival
EC	Endocrine therapy
HER2	Human epidermal growth factor 2
HR	Hazard ratio
IDC	Invasive duct carcinoma of no special type
IHC	Immunohistochemistry
ILC	Invasive lobular carcinoma
LVI	Lymphovascular invasion
OR	Odds ratio
OS	Overall survival
SBR	Scarff, Bloom, and Richardson

Introduction

Invasive lobular carcinoma (ILC) is, next to invasive duct carcinoma of no special type (IDC), the second most common histologic breast cancer subtype and represents approximately 10% of all breast cancers [1]. ILC has been shown to display distinct biological features that are correlated with specific clinical and prognostic outcomes [1–3]. ILC presents most frequently with low or intermediate grade, expresses estrogen and progesterone receptors, rarely expresses human epidermal growth factor 2 (HER2), and belongs to the luminal molecular subtype of

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10549-019-05160-9) contains supplementary material, which is available to authorized users.

✉ Alexandre de Nonneville
alexandredenonneville@gmail.com

Extended author information available on the last page of the article

breast cancer [4]. When analyzed by multigene prognostic signatures, ILC is only rarely considered as a high-risk poor prognosis disease, warranting adjuvant chemotherapy, CT [5–8]. Accordingly, and even though data are far from being homogenous on this point, ILC has often been considered a more indolent disease that is more responsive to endocrine therapy (ET) and has a better prognosis than IDC. In addition, a large number of retrospective studies have documented a poor response to cytotoxic agents in ILC receiving neoadjuvant CT [9–12]. Altogether, these data have made many oncologists relatively reluctant to administer CT in early breast cancer of ILC subtype, even though no consensus guidelines recommends to integrate the ILC subtype as an element of therapeutic decisions in the adjuvant setting. Nevertheless, published randomized clinical trials evaluating the effectiveness of CT have not reported outcomes separately based on histologic subtype [13, 14] and the established modest benefit of neoadjuvant CT in ILC may not be extrapolated to adjuvant setting since pathological complete remission has no prognostic value in ILC breast cancer [15]. Thus, benefits of CT in ILC are still unclear.

Since a large majority of ILC are hormone receptor-positive tumors [1, 4, 16] and derive clinical benefit from ET [17] to a greater magnitude than IDC [18], we examined the impact of CT on disease-free survival (DFS) and overall survival (OS) in patients receiving adjuvant ET for pure ILC of the breast, extracted from a large, multi-institutional, retrospective cohort (Fig. 1).

Patients and methods

Study design and data source

We conducted a retrospective analysis of 23,319 patients who underwent breast cancer resection with sentinel lymph node biopsy and/or axillary lymph node dissection in 15 academic French cancer centers between 1990 and 2014. Patients were included if they had histologically proven pure lobular carcinoma (i.e., excluding ductal, mixed, or non-lobular histological subtypes), expression of hormone receptors (≥ 10% of cancer cells expressing ER/PR by immunohistochemistry (IHC), as defined in the French guidelines), and received adjuvant ET. Any patients who received neoadjuvant treatment of any type, hormonal or CT, or with HER2-positive tumors (identified by IHC +/− fluorescent in situ hybridization) [19], were excluded (Fig. 1). We then analyzed the following parameters: age at diagnosis, tumor size, lymph node involvement, Scarff, Bloom, and Richardson (SBR) grade, lymphovascular invasion (LVI; based on the examination of hematoxylin–eosin-stained slides), type of surgery, adjuvant radiotherapy, period of diagnosis, and CT, which was not standardized among sites but in line with

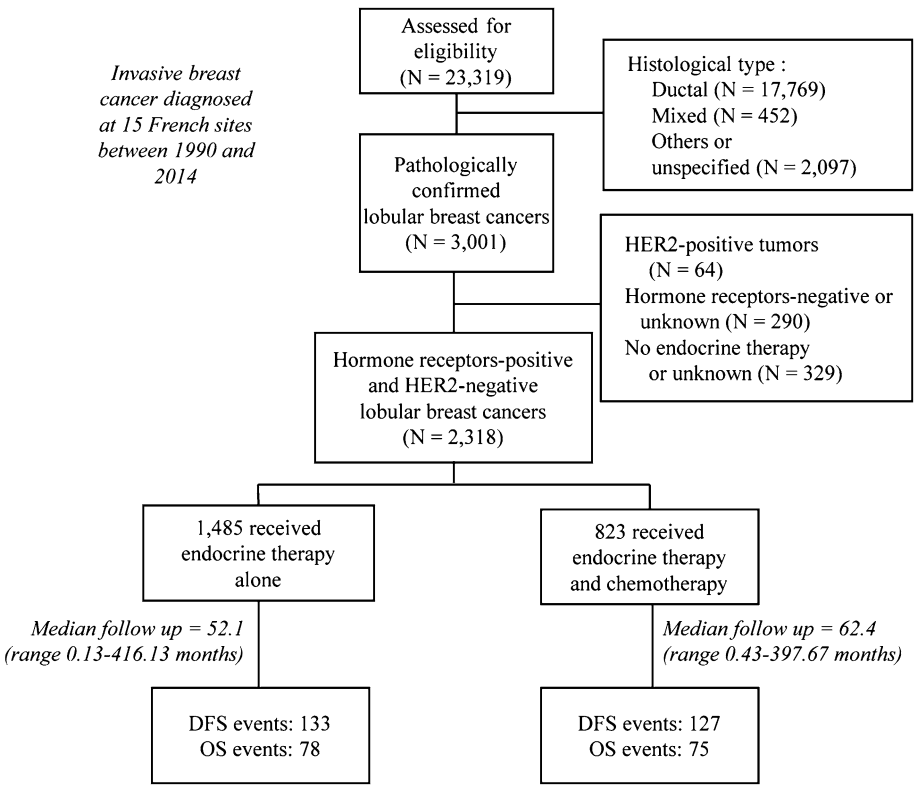

Fig. 1 Patient flow diagram showing selection of patients with hormone receptor-positive and HER2-negative lobular breast cancer. *DFS* disease-free survival, *OS* overall survival

European standards and recommendations of the time. This study was authorized by the review board of the French Society of Surgical Oncology.

Statistical analysis

Categorical variables were described using counts and frequencies, and quantitative variables were described using medians and ranges. Patients' characteristics were compared with χ^2 test for discrete variables and rank-Wilcoxon's tests for continuous variables. Main characteristics of patients and tumors (age 41 to 69 years vs. ≤ 40 years or ≥ 70 years, tumor size ≤ 20 mm vs. > 20 mm, nodal status N0, N0(i+), and pN1(mi) vs. pN1, SBR grade 1 vs. 2–3, and period of diagnosis < 1999 vs. ≥ 1999) were categorized. In order to evaluate the effect of CT, patients were divided in two groups. The first group received ET alone, while the second received a combination of ET and CT. DFS was defined as the time from surgery to breast, node, distant relapse, or death from any cause. OS was defined as the time from surgery to death from any cause. Survival curves for DFS and OS rates were generated using the Kaplan–Meier method and compared with log-rank tests. Prognostic impact of the different clinico-biological factors was tested by a multivariate Cox regression model including the following covariates categorized as mentioned above: age, tumor size, nodal status, LVI, grade, type of surgery, radiotherapy, period, and CT. A propensity score for receiving CT was estimated including the same covariates categorized as mentioned above using a caliper of 0.2 [20]. Patients with CT were then matched on this score to patients without CT using nearest-neighbor matching without replacement. The impact of CT on DFS and OS was assessed on this matched population by log-rank tests stratified on the pairs [21], and also on the original sample by Cox regression analysis including as covariates the propensity score as a continuous variable and the indicator of CT administration [22, 23]. A detailed description of the propensity score matching is provided in Supplementary Fig. 1.

In order to assess if different subgroups of patients would potentially derive more and less benefit from CT, a points-based risk score was established using a logistic regression to determine factors associated with DFS and OS events in untreated patients. According to the hazard ratio (HR), patients were classified as low or high risk of event. DFS and OS were examined in the low- or high-risk groups with or without CT in a Cox regression.

The level of statistical significance was set at $\alpha = 0.05$. Statistical analyses were carried out with SPSS® software version 24 and R software version 3.2.4. We followed the reporting recommendations specified in the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Statement [24].

Results

Characteristics of the study population

A total of 2318 patients with pure lobular, hormone receptor-positive, HER2-negative tumors, treated with adjuvant ET were identified. In this population, 1485 patients (64%) received adjuvant ET alone and 823 (36%) received adjuvant ET and CT. Baseline characteristics differed by subgroups (Table 1). Compared with patients who received ET alone, patients who received ET + CT presented significantly more adverse prognostic features, such as young age (median 55 vs. 62 years, $p < 0.001$), larger tumor size (64 vs. 22% > 20 mm, $p < 0.001$), high grade (79 vs. 71% SBR grades 2–3, $p < 0.001$), macroscopic lymph node involvement (60 vs. 8% pN1, $p < 0.001$), and LVI (19 vs. 6%, $p < 0.001$). Patient with CT received more adjuvant radiotherapy (94 vs. 89%, $p < 0.001$) and underwent more frequently mastectomy (48 vs. 18%, $p < 0.001$).

Disease-free survival (DFS)

As of October 2017, the median follow-up of patients with ET + CT and ET alone were 65.38 months (95% confidence interval CI [62.18–68.57]) and 54.29 months (95% CI [51.88–56.71]), respectively. A total of 260 DFS events (11%, 127 in ET + CT group and 133 in ET alone group) were observed and the 10-year estimates DFS was 76% (95% CI [74.4–77.8%]) in the overall population. In univariate analysis, CT was not associated with a DFS benefit (HR = 1.34 [1.02–1.71]), with 10-year estimates DFS of 75% (95% CI [71.7–77.7%]) versus 76% (95% CI [73.9–78.3%]) in ET + CT and ET groups, respectively. In multivariate analysis (Table 2) including the criteria significantly associated with CT prescription (Supplementary Table 1), DFS was significantly improved by the adjunction of CT to ET (HR = 0.61, 95% CI [0.41–0.90]; $p = 0.01$) (Fig. 2). Results were consistent when the propensity score was considered in the adjusted analyses (HR = 0.36, 95% CI [0.21–0.60]; $p < 0.001$) (Fig. 3) and 10-year estimates DFS in patient case-matched for propensity score analysis were 90% (95% CI [87–93.4%]) in the ET + CT group versus 66% (95% CI [61.4–71.4%]) with ET alone (Fig. 2).

Overall survival (OS)

Death occurred in 153 patients (7%, 75 in ET + CT group and 78 in ET alone group). Ten-year OS was 84% (95% CI [82.9–85.9%]) in the overall population. There was no significant OS benefit of CT in univariate analysis (HR = 1.29 [0.93–1.77], $p = 0.125$, log-rank test) with 10-year estimates

Table 1 Patients and tumor characteristics at baseline

	Total		Endocrine therapy only ($n=1485$)		Endocrine therapy with chemotherapy ($n=823$)		p values (χ^2 or Wilcoxon)
	N	%	*N*	%	*N*	%	
Age (years)							
Median [min–max]	60	[29–90]	61, 85	[34–90]	55	[29–88]	< 0.001
41–69	1824	79	1110	74	714	87	< 0.001
≤ 40	48	2	14	1	34	4	
≥ 70	446	19	371	25	75	9	
Tumor size							< 0.001
≤ 20 mm	1455	63	1161	78	294	36	
> 20 mm	839	37	318	22	521	64	
Nodal status							< 0.001
pN0	1505	65	1259	84	246	30	
pN0 (i+)	94	4	65	4	29	4	
pN1 (mi)	103	4	52	3	51	6	
pN1	616	27	119	8	497	60	
Grades							< 0.001
1	588	26	416	29	172	21	
2	1534	68	979	68	555	69	
3	119	5	41	3%	78	10	
LVI							< 0.001
Absent	1774	89	1183	94	591	81	
Present	225	11	82	6	143	19	
Surgery							< 0.001
Breast conserving	1652	71	1220	82	432	52	
Mastectomy	666	29	275	18	391	48	
Radiotherapy							< 0.001
No	202	9	156	11	46	6	
Yes	2014	91	1240	89	774	94	
Period							0.301
< 1999	190	8	116	8	74	9	
≥ 1999	2128	92	1379	92	749	91	

Percentages are calculated in relation to the number of available data

LVI lymphovascular invasion

Table 2 Multivariate analysis including age, tumor size, nodal status, lymphovascular invasion, Scarff, Bloom and Richardson grade, type of surgery, use of radiotherapy, period of diagnosis, and chemotherapy

	DFS				OS			
	OR	[95% CI]		p values	OR	[95% CI]		p values
		Min	Max			Min	Max	
Age	1.46	1.21	1.76	< 0.001	1.63	1.27	2.09	< 0.001
Tumor size	1.88	1.36	2.59	< 0.001	2.24	1.44	3.49	< 0.001
Nodal status	1.40	1.22	1.59	< 0.001	1.66	1.38	2.00	< 0.001
LVI	1.69	1.21	2.35	< 0.001	1.51	0.98	2.31	0.06
Grade	1.21	0.92	1.58	0.18	1.24	0.86	1.79	0.26
Surgery	1.29	0.93	1.79	0.13	1.25	0.82	1.90	0.29
Radiotherapy	1.06	0.57	1.98	0.85	0.97	0.43	2.19	0.95
Period	0.85	0.72	1.00	0.05	0.80	0.65	0.97	0.03
Chemotherapy	0.61	0.41	0.90	0.01	0.52	0.31	0.87	0.01

DFS disease-free survival, *OS* overall survival, *OR* odds ratio, *CI* confidence interval, *LVI* lymphovascular invasion

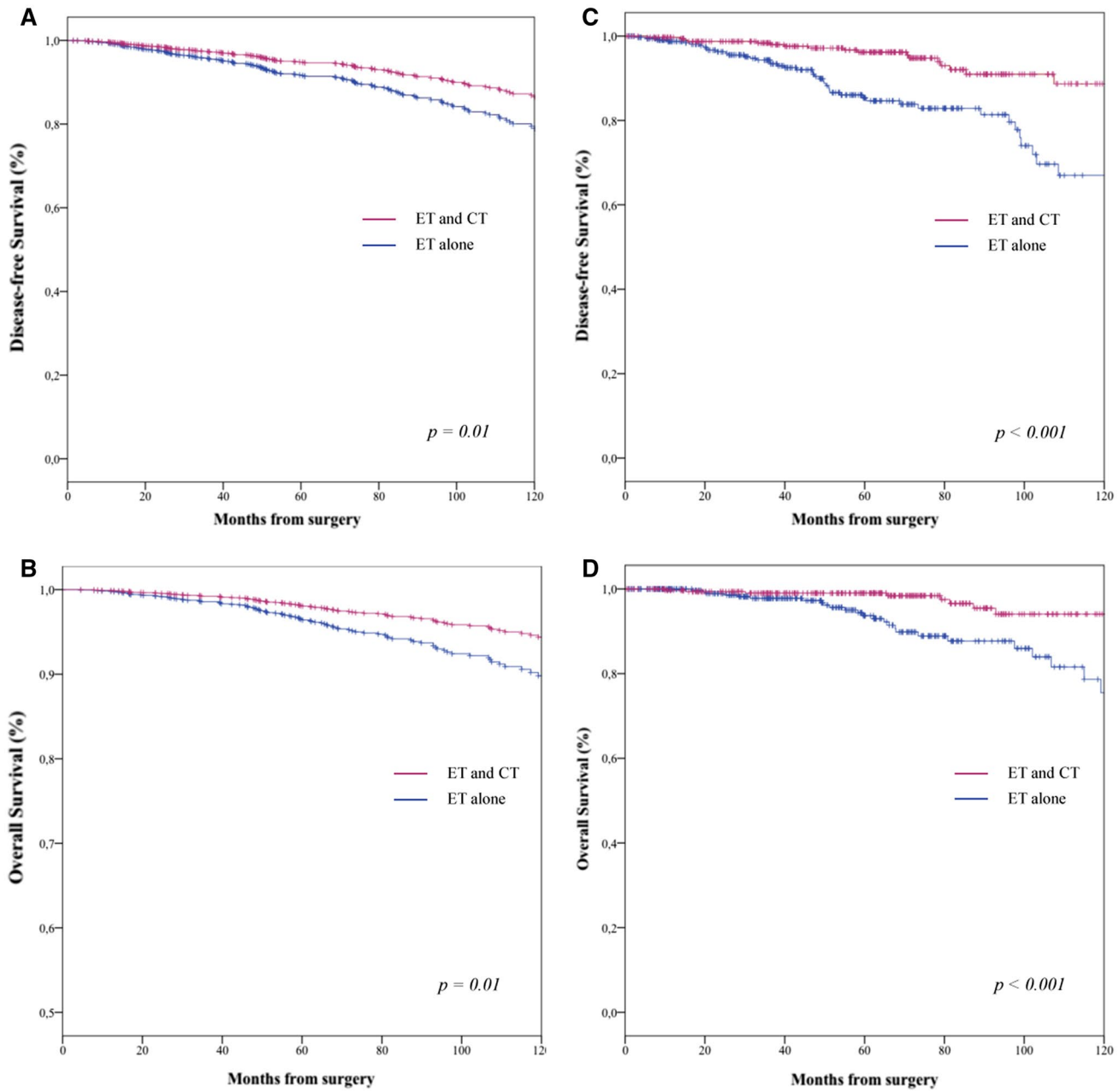

Fig. 2 Cox-adjusted curves of disease-free and overall survival among patients treated and untreated by chemotherapy (**a, b**) and Kaplan–Meier estimates among patients' case-matched for propensity score treated and untreated by chemotherapy (**c, d**). *ET* endocrine therapy, *CT* adjuvant chemotherapy

OS of 84% [81.2–86.2%] in ET + CT group versus 83% [81.3–85.1%] in ET alone group. In multivariate analysis (Table 2), OS was significantly impacted by the adjunction of CT to ET (HR = 0.52, 95% CI [0.31–0.87]; $p = 0.01$) (Fig. 2). As DFS, results of OS between the two groups were consistent when the propensity score was considered in the adjusted analyses (HR = 0.20, 95% CI [0.09–0.43]; $p < 0.001$) (Fig. 3) and 10-year estimates OS in patient case-matched for propensity score analysis were 96% (95% CI [93.8–98%]) in the ET + CT group versus 71% (95% CI [66.6–76.2%]) with ET alone (Fig. 2).

Subgroup analysis

Tumor size, macroscopic lymph node involvement, and LVI were independently associated with DFS and OS events in a logistic regression including untreated patients (Supplementary Table 2). According to the HRs magnitude,

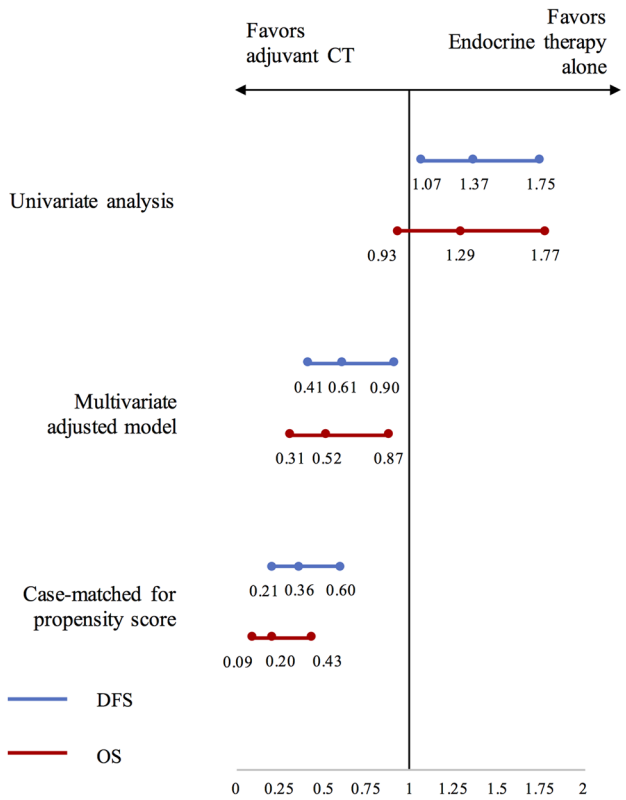

Fig. 3 Analysis of disease-free survival and overall survival: summary of hazard ratios. *CT* adjuvant chemotherapy, *DFS* disease-free survival, *OS* overall survival

a points-based risk score was built (pN1 = 6 pts, tumor size > 2 cm = 3 pts, and LVI = 2 pts). Patients with a score under five were assigned to the low-risk group ($n = 1398$, 70%) and patients with a score ranging from 5 to 11 were assigned to the high-risk group ($n = 588$, 30%). Thus, patients in the high-risk group had either macroscopic lymph node involvement, or a tumor size over 20 mm and LVI, or macroscopic lymph node involvement, going either with one or both risk factors.

Comparing to low-risk patients with CT, low-risk patients without CT did not have significant differences in DFS or OS (Table 3; Supplementary Fig. 2). In the high-risk group, patients with CT had DFS (HR = 0.52 [0.36–0.75]; $p < 0.001$) and OS benefit (HR = 0.37 [0.24–0.57]; $p < 0.001$) comparing to high-risk patients without CT.

Discussion

We examined the survival of patients receiving adjuvant ET for pure invasive lobular breast carcinoma in a large, national, multi-institutional, retrospective cohort and found that patients receiving additional CT derived significant DFS as well as OS benefits. Since treated patients had more unfavorable baseline characteristics, the effect of CT was not apparent in univariate analysis. We therefore conducted multivariate analyses, including a propensity score.

Two main studies have attempted to evaluate the impact of CT in hormone receptor-positive lobular early breast cancer and did not report benefits of CT [25, 26]. Authors hypothesized that CT is associated with minimal-added benefit for patients with ILC breast cancer who receive ET based on the low response of ILC observed in the neoadjuvant setting [9–12]. This argument could be criticized since pathological complete remission has no prognostic value in ILC breast cancer [15]. Thus, Truin et al. [25] have retrospectively examined the effect of CT in a multicenter cohort of postmenopausal women (aged 50–75 years) with ILC breast cancer and found no additional beneficial effects of CT addition to ET with 10-year OS rate at 68% in ET group and 66% in ET + CT group (HR = 1.00 [0.82–1.21], $p = 0.97$). More recently, Marmor et al. [26] analyzed a large cohort of patients extracted from the California Cancer Registry and reported a 10-year OS rate of 84% for the ET alone group and 83% for the ET + CT group. While our results in univariate analysis are very close to those of Marmor et al., the reasons for such important discordance with Truin et al. could be explained by the very large proportion of patients treated before year 2000 in their cohort. Indeed, global management of malignancies improved due to the incorporation of taxanes and earlier diagnosis [27]. In the present study, we observed a beneficial effect of addition of CT to ET on DFS and OS in multivariate Cox model (HR = 0.61, 95% CI

Table 3 Multivariate analysis including low- or high-risk group with or without chemotherapy

	DFS				OS			
	HR	[95% CI]		*p* values	HR	[95% CI]		*p* values
		Min	Max			Min	Max	
Low-risk group with CT $n = 273$ (14%)	Reference category				Reference category			
Low-risk group without CT $n = 1125$ (57%)	1.50	0.84	2.67	0.167	2.26	0.79	6.43	0.126
High-risk group with CT $n = 457$ (23%)	3.77	2.15	6.63	< 0.001	7.47	2.71	20.60	< 0.001
High-risk group without CT $n = 131$ (7%)	7.57	4.13	13.87	< 0.001	20.04	7.12	56.41	< 0.001

DFS disease-free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval, *CT* chemotherapy

[0.41–0.90], $p=0.01$ and 0.52, 95% CI [0.31–0.87], $p=0.01$, respectively). This effect was even more pronounced when propensity score matching, aiming to compensate for baseline characteristics, was used. Although multivariate analysis was carried out in Truin and Marmor studies, several potentially important variables such as period of diagnosis, LVI, precise nodal status (Marmor et al.), HER2 status, adjuvant radiotherapy, or type of surgery (Truin et al.) were not studied. Thereby, Truin et al. and Marmor et al. reported HR were 1.00 [0.82–1.21], $p=0.965$ and 1.18 [0.90–1.54], $p=0.21$, respectively. Another reason for the observed discordance between the results of these studies and our own data may include the important molecular heterogeneity of ILC, as described in a recent genomic study [28]. Indeed, the large number of molecular alterations observed in this subtype may be associated with distinct patterns of sensitivity to CT, thereby contributing to a variable prognostic impact of CT. We describe here a significantly larger number of patients categorized in the high-risk group according to clinical characteristics than reported in the literature with the use of genomic tests. Nevertheless, the role of these tests has not been clearly defined for ILC and could underestimate the risk by ignoring LVI or, for some of them, pN status [6–8].

One intriguing question raised by our results is how such a poorly responding disease when treated in the neoadjuvant setting may derive a significant benefit to CT? A similar uncoupling between efficacy in terms of pCR and outcome was also observed in the response-guided neoadjuvant CT GeparTrio study [29]. In this trial, intensifying CT in early responders or switching it to an alternative regimen in non-responders failed to improve pCR, whereas this intervention was unexpectedly associated with an improved survival outcome. Notably, the survival benefit was restricted to luminal disease, including luminal A subtypes in which pCR had no prognostic impact on survival. Similar to our data in ILC, a highly luminal disease, these results suggest that CT may have antitumor effect on micrometastatic disease, irrespective of the observed effects on primary tumors. In a current environment where more and more patients with luminal A breast cancer are identified as not likely to benefit from CT, identifying high-risk subtypes of ILC that do still benefit from CT would be worth. The vast majority of ILC tested via Oncotype DX are at low or intermediate risk. Only 1.5 to 2.8% (up to 8% as per the TAILORx RS cutoffs) of ILC are classified as high risk, versus 16.9–32.2% for IDC [6, 7, 30–33]. According to a clinicopathological score proposed in our study, we categorized up to 30% of ILC patient as high risk with a large HR benefit for CT. These results suggest that Oncotype DX may not be sufficient to determine which subset of ILC would benefit from CT.

Despite careful methodology aimed at minimizing treatment selection bias, some limitations of our study have to be considered. These limitations are inherent in the retrospective design of the study with potential selection bias and lack of standardization in treatment strategies. Our inclusion period covering a period of 24 years, patients have probably been receiving different types and durations of adjuvant endocrine treatment and different CT regimens. Since the relative effectiveness of aromatase inhibitors compared with tamoxifen is higher for ILC [18], type of ET could be a confounding factor why CT was particularly beneficial for young or high-risk women. In addition, it is a non-randomized study with possible indication bias, in which treated and untreated patients have different prognostic features. However, we performed several approaches to adjust baseline differences and to reduce the impact of treatment selection bias, including multivariate Cox model and propensity score matching. Finally, no central pathology review was undertaken and specific subtypes of ILC, which may have improved outcomes with CT, such as pleomorphic lobular carcinoma, could not have been excluded. Nevertheless, data were collected from reference centers and tumor features were analyzed by highly trained and national expert pathologists.

In conclusion, we found that patients receiving adjuvant ET for pure invasive lobular breast carcinoma may derive significant DFS as well as OS benefits from CT. At least, within the limits of a retrospective study, our results highlight that patients with high-risk ILC should not be denied CT because of such histologic subtype and lead to the open-ended question about clinical score versus gene expression signature for ILC CT triage.

Funding This academic work did not receive financial support from any funding source.

Author contributions AN, CJ, AG, and GH contributed to literature search, figures, study design, data analysis, data interpretation, and writing. All authors have participated in the data collection. All authors have critically reviewed the final version of the manuscript and approved its content. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. *Conceptualization* AN, CJ, AG, GH. *Data curation* AN, CJ, AG, JMC, MC, FR, CM, MPC, NC, PEC, EJ, ED, RR, CC, PG, ASA, CT, EL, GH. *Formal analysis* AN, CJ, AG, GH. *Investigation* AN, CJ, AG, GH. *Methodology* AN, CJ, AG, GH. *Project administration* AN. *Supervision* AG, GH. *Validation* AN, CJ, AG, JMC, MC, FR, CM, MPC, NC, PEC, EJ, ED, RR, CC, PG, ASA, CT, EL, GH. *Visualization* AN, CJ, AG, JMC, MC, FR, CM, MPC, NC, PEC, EJ, ED, RR, CC, PG, ASA, CT, EL, GH. *Writing* AN, CJ, AG, GH. *Review and editing* AN, CJ, AG, JMC, MC, FR, CM, MPC, NC, PEC, EJ, ED, RR, CC, PG, ASA, CT, EL, GH.

Compliance with ethical standards

Conflict of interest Authors have nothing to disclose.

Ethical Approval All procedures performed in this study involving human participants were done in accordance with the French Ethical Standards and with the 2008 Helsinki Declaration. As this was

a retrospective non-interventional study, no formal personal consent was required.

References

1. Arpino G, Bardou VJ, Clark GM, Elledge RM (2004) Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. Breast Cancer Res 6:R149
2. Martinez V, Azzopardi JG (1979) Invasive lobular carcinoma of the breast: incidence and variants. Histopathology 3:467–488
3. Korkola JE, DeVries S, Fridlyand J, Hwang ES, Estep ALH, Chen Y-Y, Chew KL, Dairkee SH, Jensen RM, Waldman FM (2003) Differentiation of lobular versus ductal breast carcinomas by expression microarray analysis. Cancer Res 63:7167–7175
4. Pestalozzi BC, Zahrieh D, Mallon E, Gusterson BA, Price KN, Gelber RD, Holmberg SB, Lindtner J, Snyder R, Thürlimann B et al (2008) Distinct clinical and prognostic features of infiltrating lobular carcinoma of the breast: combined results of 15 International Breast Cancer Study Group clinical trials. J Clin Oncol Off J Am Soc Clin Oncol 26:3006–3014
5. Bertucci F, Orsetti B, Nègre V, Finetti P, Rougé C, Ahomadegbe J-C, Bibeau F, Mathieu M-C, Treilleux I, Jacquemier J et al (2008) Lobular and ductal carcinomas of the breast have distinct genomic and expression profiles. Oncogene 27:5359–5372
6. Kizy S, Huang JL, Marmor S, Tuttle TM, Hui JYC (2017) Impact of the 21-gene recurrence score on outcome in patients with invasive lobular carcinoma of the breast. Breast Cancer Res Treat 165:757–763
7. Felts JL, Zhu J, Han B, Smith SJ, Truica CI (2017) An analysis of Oncotype DX recurrence scores and clinicopathologic characteristics in invasive lobular breast cancer. Breast J 23:677–686
8. Singh K, He X, Kalife ET, Ehdaivand S, Wang Y, Sung CJ (2018) Relationship of histologic grade and histologic subtype with oncotype Dx recurrence score; retrospective review of 863 breast cancer oncotype Dx results. Breast Cancer Res Treat 168:29–34
9. Delpech Y, Coutant C, Hsu L, Barranger E, Iwamoto T, Barcenas CH, Hortobagyi GN, Rouzier R, Esteva FJ, Pusztai L (2013) Clinical benefit from neoadjuvant chemotherapy in oestrogen receptor-positive invasive ductal and lobular carcinomas. Br J Cancer 108:285–291
10. Cristofanilli M, Gonzalez-Angulo A, Sneige N, Kau S-W, Broglio K, Theriault RL, Valero V, Buzdar AU, Kuerer H, Buccholz TA et al (2005) Invasive lobular carcinoma classic type: response to primary chemotherapy and survival outcomes. J Clin Oncol 23:41–48
11. Tubiana-Hulin M, Stevens D, Lasry S, Guinebretière JM, Bouita L, Cohen-Solal C, Cherel P, Rouëssé J (2006) Response to neoadjuvant chemotherapy in lobular and ductal breast carcinomas: a retrospective study on 860 patients from one institution. Ann Oncol Off J Eur Soc Med Oncol 17:1228–1233
12. Cocquyt VF, Blondeel PN, Depypere HT, Praet MM, Schelfhout VR, Silva OE, Hurley J, Serreyn RF, Daems KK, Van Belle SJP (2003) Different responses to preoperative chemotherapy for invasive lobular and invasive ductal breast carcinoma. Eur J Surg Oncol 29:361–367
13. Fisher B, Dignam J, Bryant J, DeCillis A, Wickerham DL, Wolmark N, Costantino J, Redmond C, Fisher ER, Bowman DM et al (1996) Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. J Natl Cancer Inst 88:1529–1542
14. Early Breast Cancer Trialists' Collaborative Group, EBCTCG (2012) Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials. Lancet 379:432–444
15. von Minckwitz G, Untch M, Blohmer J-U, Costa SD, Eidtmann H, Fasching PA, Gerber B, Eiermann W, Hilfrich J, Huober J et al (2012) Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 30:1796–1804
16. Coradini D, Pellizzaro C, Veneroni S, Ventura L, Daidone MG (2002) Infiltrating ductal and lobular breast carcinomas are characterised by different interrelationships among markers related to angiogenesis and hormone dependence. Br J Cancer 87:1105–1111
17. Rakha EA, El-Sayed ME, Powe DG, Green AR, Habashy H, Grainge MJ, Robertson JFR, Blamey R, Gee J, Nicholson RI et al (2008) Invasive lobular carcinoma of the breast: response to hormonal therapy and outcomes. Eur J Cancer 44:73–83
18. Metzger Filho O, Giobbie-Hurder A, Mallon E, Gusterson B, Viale G, Winer EP, Thürlimann B, Gelber RD, Colleoni M, Ejlertsen B et al (2015) Relative effectiveness of letrozole compared with tamoxifen for patients with lobular carcinoma in the BIG 1-98 Trial. J Clin Oncol Off J Am Soc Clin Oncol 33:2772–2779
19. Penault-Llorca F, Balaton A, Sabourin J-C, Le Doussal V (2002) Groupe d'évaluation des facteurs pronostiques par immunohistochimie dans les cancers du sein (GEFPICS) [Immunochemistry evaluation of HER2 status in infiltration breast cancer: technical protocol and interpretation guidelines]. Ann Pathol 22:150–157
20. Thoemmes F (2012) Propensity score matching in SPSS. ArXiv12016385 Stat
21. Klein J, Moeschberger M, Hawkins K (2004) Survival analysis: techniques for censored and truncated data. Pharm Stat 3:303–304
22. Rosenbaum PR, Rubin DB (1983) The central role of the propensity score in observational studies for causal effects. Biometrika 70:41
23. Rosenbaum PR (1987) Model-based direct adjustment. J Am Stat Assoc 82:387–394
24. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M, STROBE Initiative (2007) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLoS Med 4:e297
25. Truin W, Voogd AC, Vreugdenhil G, van der Heiden-van der Loo M, Siesling S, Roumen RM (2012) Effect of adjuvant chemotherapy in postmenopausal patients with invasive ductal versus lobular breast cancer. Ann Oncol Off J Eur Soc Med Oncol 23:2859–2865
26. Marmor S, Hui JYC, Huang JL, Kizy S, Beckwith H, Blaes AH, Rueth NM, Tuttle TM (2017) Relative effectiveness of adjuvant chemotherapy for invasive lobular compared with invasive ductal carcinoma of the breast. Cancer 123:3015–3021
27. De Laurentiis M, Cancello G, D'Agostino D, Giuliano M, Giordano A, Montagna E, Lauria R, Forestieri V, Esposito A, Silvestro L et al (2008) Taxane-based combinations as adjuvant chemotherapy of early breast cancer: a meta-analysis of randomized trials. J Clin Oncol 26:44–53
28. Desmedt C, Zoppoli G, Gundem G, Pruneri G, Larsimont D, Fornili M, Fumagalli D, Brown D, Rothé F, Vincent D et al (2016) Genomic characterization of primary invasive lobular breast cancer. J Clin Oncol 34:1872–1881
29. von Minckwitz G, Blohmer JU, Costa SD, Denkert C, Eidtmann H, Eiermann W, Gerber B, Hanusch C, Hilfrich J, Huober J et al (2013) Response-guided neoadjuvant chemotherapy for breast cancer. J Clin Oncol 31:3623–3630
30. Albain KS, Barlow WE, Shak S, Hortobagyi GN, Livingston RB, Yeh I-T, Ravdin P, Bugarini R, Baehner FL, Davidson NE et al (2010) Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy:

a retrospective analysis of a randomised trial. Lancet Oncol 11:55–65
31. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, Geyer CE, Dees EC, Goetz MP, Olson JA et al (2018) Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med 379:111–121
32. Kizy S, Huang JL, Marmor S, Tuttle TM, Hui JYC (2017) Impact of the 21-gene recurrence score on outcome in patients with invasive lobular carcinoma of the breast. Breast Cancer Res Treat 165:757–763. https://doi.org/10.1007/s10549-017-4355-9
33. Tsai ML, Lillemoe TJ, Finkelstein MJ, Money JE, Susnik B, Grimm E, et al (2016) Utility of oncotype DX risk assessment in patients with invasive lobular carcinoma. Clin Breast Cancer 16:45–50. https://doi.org/10.1016/j.clbc.2015.08.001

Affiliations

Alexandre de Nonneville[1] · Camille Jauffret[2] · Anthony Gonçalves[1] · Jean-Marc Classe[3] · Monique Cohen[2] · Fabien Reyal[4] · Chafika Mazouni[5] · Marie-Pierre Chauvet[6] · Nicolas Chopin[7] · Pierre-Emmanuel Colombo[8] · Eva Jouve[9] · Emile Darai[10] · Roman Rouzier[11] · Charles Coutant[12] · Pierre Gimbergues[13] · Anne-Sophie Azuar[14] · Christine Tunon de Lara[15] · Eric Lambaudie[2] · Gilles Houvenaeghel[2]

1 Department of Medical Oncology, Aix-Marseille Univ, CNRS, INSERM, Institut Paoli-Calmettes, CRCM, 232 Bd. Sainte-Marguerite, 13009 Marseille, France
2 Department of Surgical Oncology, Aix-Marseille Univ, CNRS, INSERM, Institut Paoli-Calmettes, CRCM, Marseille, France
3 Institut René Gauducheau, Site hospitalier Nord, St Herblain, France
4 Institut Curie, 26 rue d'Ulm 75248, Paris, France
5 Institut Gustave Roussy, 114 rue Edouard Vaillant, Villejuif, France
6 Centre Oscar Lambret, 3 rue Frédéric Combenal, Lille, France
7 Centre Léon Bérard, 28 rue Laennec, Lyon, France
8 Centre Val d'Aurelle, Montpellier, France
9 Centre Claudius Regaud, 20-24 rue du Pont St Pierre, Toulouse, France
10 Hôpital Tenon, 4 rue de la Chine, Paris, France
11 Centre René Huguenin, 35 rue Dailly, Saint Cloud, France
12 Centre Georges François Leclerc, 1 rue du Professeur Marion, Dijon, France
13 Centre Jean Perrin, 58 rue Montalembert, Clermont-Ferrand, France
14 Chemin de Clavary, Hôpital de Grasse, Grasse, France
15 Institut Bergonié, 229 Cours de l'Argonne, Bordeaux, France