




Invasive Lobular Carcinoma of the Breast: Toward Tailoring Therapy?

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In this issue of the Journal, Oesterreich and colleagues (1) report on the results of a retrospective multicenter analysis of the clinicopathological features and outcomes of patients diagnosed with invasive lobular carcinoma (ILC) breast cancer.

Invasive lobular carcinoma (ILC) is the second most common histological type of breast cancer, accounting for 5%-15% of all breast carcinomas (2). ILC is characterized by a proliferation of discohesive tumor cells, arranged in single files or as individual single cells. In most cases, this lack of intercellular adhesion is due to the loss of E-cadherin expression, secondary to the mutational or epigenetic inactivation of its encoding gene, *CDH1*. The critical role of *CDH1* inactivation in the pathogenesis of ILC has been supported by genetically engineered mouse models (3) and observations made in germline *CDH1* mutation carriers. Beyond their morphological pattern and association with *CDH1* inactivation, ILC displays no pathognomonic pathological or clinical feature. However, comparing ILC with invasive breast carcinoma of no special type (IBC-NST, formerly known as invasive ductal carcinoma [IDC]) could inform on clinically relevant associations that may be useful for ILC management, as currently ILC has so far been managed in a similar manner to that of IBC-NST. In that context, using available pathological and clinical reports from more than 30 000 consecutive breast cancer patients, collected in 3 US institutions over a 28-year period (Great Lakes Breast Cancer Consortium), Oesterreich and colleagues compared ILC (n = 3617) patients with IBC-NST (n = 30 045) patients.

Their initial analyses investigated differences in clinical and pathological features at diagnosis. In this series, compared with IBC-NST, the age at diagnosis of ILC was slightly higher (61 vs 57 years in IBC-NST). ILC also had a higher stage at diagnosis (stage III: 17.0% vs 8.0%, lymph node involvement (N2 and N3: 9.9% vs 5.5%), and a larger tumor size (T3 and T4: 14.7% vs 4%; de novo stage IV: 3.7% vs 2.4%) despite a lower grade (grade 1 and 2: 88% vs 60%). ILC also had a higher frequency of bone and peritoneal metastasis and a lower frequency of lung metastasis. An important finding is that all the clinical differences mentioned above remained statistically significant when the

comparison was restricted to estrogen receptor (ER)-positive tumors only, which indicates that the clinical specificities of ILC are not related to their intrinsic subtype but, above all, to their histo-molecular peculiarities. Overall, such findings confirm prior observations (4), partly stemming from the well-described lower sensitivity of screening imaging tools. However, because of its size and because the 3 participating institutions share common standard of care and diagnoses procedures for patients' management, the report by Oesterreich and colleagues (1) brings further robust evidence of the clinical specificities of ILC. A further step for this study could be a central pathological review for a harmonized definition of ILC cases and determination of the E-cadherin status that will overcome the limitations of the present analysis, based on retrospective diagnoses.

In a second series of analyses, Oesterreich and colleagues (1) describe treatment patterns and patient outcomes, data that are often missing in retrospective studies with no direct access to patient files. In keeping with the larger tumor size at diagnosis, more ILC patients underwent a mastectomy (60% in ILC vs 50% in IBC-NST). Concerning the other treatments, patients with ILC received less radiation therapy compared with patients with IBC-NST (52% vs 57% and 68% vs 77% when excluding patients who underwent mastectomies), whereas in the ER-positive subgroup, endocrine therapy was used more frequently (90% vs 87%), with a similar administration of chemotherapy (41% in both).

There is conflicting evidence on the prognosis of ILC [discussed in (5)], but previous studies with sufficient follow-up have shown that ILC has worse long-term outcome compared with IBC-NST because of late recurrences (6-9). In that regard, Oesterreich and colleagues (1) reported patient outcomes after a median follow-up of 66 (range = 0-345) months. In univariate analysis, patients with ILC had a somehow similar long-term breast cancer-free interval (referred to as "disease-free survival" [DFS] by the authors) than patients with IBC-NST. When restricting the analysis to ER-positive tumors only, the authors were able to confirm ER-positive ILC is a statistically significant unfavorable prognostic factor (hazard ratio [HR] = 1.18, 95%

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confidence interval [CI] = 1.01 to 1.38). A visual inspection of breast cancer-free interval curves confirms that this difference is mostly because of an increased number of relapses occurring in ILC patients after 10 years of follow-up. In terms of overall survival (OS), univariate analyses showed a lower survival in ILC vs IBC-NST patients, both in the general population and in the ER-positive subgroup (HR = 1.32, 95% CI = 1.19 to 1.45). On visual inspection of OS curves [see Figure 2 in (1)], the 2 OS curves start to diverge early, before 10 years, with a constant hazard ratio over time. Data on breast cancer-specific mortality are unfortunately not available. Taken together, these findings confirm patients diagnosed with ILC have a higher risk of poor outcome and death, possibly related to adverse prognostic factors but also to older age at diagnosis.

Using survival data from their large cohort, Oesterreich et al. (1) were then able to report 2 newer aspects related to ILC clinical specificities: 1) the outcome of ILC patients who had their tumor Recurrence Score Oncotype DX (RS) determined (per routine care) and 2) whether the outcome of ILC and IBC-NST differs when receiving the same treatments at early stage. Regarding the RS, determined in 580 ER-positive ILC and 3123 ER-positive IBC-NST patients, the authors note that patients with ILC classified as high risk had no relapse, with no statistically significant difference in outcome found between patients with high and low RS ILC. However, few patients were considered as high risk with the RS (1.9%, n = 40, vs 11% for IDC), the follow-up was low in this subcohort (48.2 months), and these patients had probably received adjuvant chemotherapy. Nevertheless, these findings are in line with several studies that observed a low rate of high-risk ILC patients (<5%-10%) with the RS, with controversial prognostic value [reviewed in (4)], even if a recent study in approximately 15 000 ILCs reported a statistically significant prognostic and predictive value of the RS (10). Therefore, to predict the prognosis for ILC patients, it might be more informative to use dedicated ILC signatures such as LobSig or other genomic tests, ILC (eg, MammaPrint, Prosigna, EPclin, Breast Cancer Index, Genomic Grade Index) and that were confirmed to be prognostic in this histological type (such as MammaPrint, EPclin ...) [reviewed in (4)]. Despite the prognostic prediction of these assays, the benefit of adding chemotherapy in the high-risk ILC group is debated in the adjuvant setting, in a general context where the benefit of chemotherapy is still discussed in ILC (11). For these reasons, the authors were surprised that the recent use of chemotherapy in the cohort was similar in patients with IDC and ILC. In high-risk ILC, extended endocrine therapy (ET) needs to be considered even if the benefit of the extension has not been formally demonstrated, and because of the late relapses (after 10 years) observed in some patients, the question of extending ET beyond 10 years is open. In this study, no data were available concerning the type of chemotherapy or ET administered and its duration.

Regarding the comparison of outcome between ILC and IBC-NST when receiving the same treatments at early stage (surgery, radiotherapy, ET, or chemotherapy), the authors performed a propensity score matching analysis between ILC and IBC-NST patients being matched on age, stage, grade, nodal status, and institution and did not observe significant differences in outcome for DFS. As the hazard ratio for DFS was less than 1 for each type of treatment despite no statistically significant P value (eg, HR = 0.8 for lumpectomy and radiation therapy), Oesterreich and colleagues (1) suggested that the treatment efficacy might be higher in ILC, but this is very hypothetical as many parameters are taken into account for the administration

of patients treatment, these parameters not being in the statistical model.

In conclusion, Oesterreich and colleagues (1) present a highly informative study for ILC. In addition, this large series of ILC paves the path for future biological and genomic analyses. In particular, a better understanding of ILC microenvironment will be crucial, as tumor-infiltrating lymphocytes showed a negative prognostic impact in ILC (12,13), and the presence of immune transcriptomic signature appears to be a biological feature defining at least a portion of lobular carcinomas (14-16). These insights will hopefully reveal new therapeutic strategies and will help set up new trials specifically dedicated to ILC. Future trials in early ILC setting will also have to provide substantial follow-up to account for the late onset of metastasis in ILC and thus assess treatment efficacy as accurately as possible. Ultimately, the complete elucidation of the mechanisms involved in lobular cell dormancy, their mechanisms of metastatic spreading, and their therapeutic targeting is an important issue to cure ILC. To overcome this situation, several consortium efforts together with patient advocacies have been created over the past few years to better characterize lobular carcinoma, such as the European Lobular Breast Cancer Consortium and the Lobular Breast Cancer Alliance in the United States, and will help improve the management of this disease in the very near future.

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Data Availability

No data were generated or analyzed for this editorial.

References

- Oesterreich S, Nasrazadani A, Zou J, et al. Clinicopathological features and outcomes comparing patients with invasive ductal and lobular breast cancer. *J Natl Cancer Inst.* 2022;114(11):1511-1522.
- Christgen M, Cserni G, Floris G, et al. Lobular breast cancer: histomorphology and different concepts of a special spectrum of tumors. *Cancers (Basel).* 2021; 13(15):3695. doi:10.3390/cancers13153695.
- Christgen M, Derksen PWB. Lobular breast cancer: molecular basis, mouse and cellular models. *Breast Cancer Res.* 2015;17(1):16. doi: 10.1186/s13058-015-0517-z.
- Van Baelen K, Geukens T, Maetens M, et al. Current and future diagnostic and treatment strategies for patients with invasive lobular breast cancer. *Ann Oncol.* 2022;33(8):769-785. doi:10.1016/j.annonc.2022.05.006.
- Guiu S, Wolfer A, Jacot W, et al. Invasive lobular breast cancer and its variants: how special are they for systemic therapy decisions? *Crit Rev Oncol Hematol.* 2014;92(3):235-257. doi:10.1016/j.critrevonc.2014.07.003.

6. Pestalozzi BC, Zahrieh D, Mallon E, et al. 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*. 2008; 26(18):3006-3014. doi:10.1200/J Clin Oncol.2007.14.9336.
7. Rakha EA, El-Sayed ME, Powe DG, et al. Invasive lobular carcinoma of the breast: response to hormonal therapy and outcomes. *Eur J Cancer*. 2008;44(1): 73-83. doi:10.1016/j.ejca.2007.10.009.
8. Adachi Y, Ishiguro J, Kotani H, et al. Comparison of clinical outcomes between luminal invasive ductal carcinoma and luminal invasive lobular carcinoma. *BMC Cancer*. 2016;16:248. doi:10.1186/s12885-016-2275-4.
9. Engström MJ, Opdahl S, Vatten LJ, Haugen OA, Bofin AM. Invasive lobular breast cancer: the prognostic impact of histopathological grade, E-cadherin and molecular subtypes. *Histopathology*. 2015;66(3):409-419. doi: 10.1111/his.12572.
10. Weiser R, Polychronopoulou E, Hatch SS, et al. Adjuvant chemotherapy in patients with invasive lobular carcinoma and use of the 21-gene recurrence score: a National Cancer Database analysis. *Cancer*. 2022;128(9):1738-1747. doi:10.1002/cncr.34127.
11. Trapani D, Gandini S, Corti C, et al. Benefit of adjuvant chemotherapy in patients with lobular breast cancer: a systematic review of the literature and meta-analysis. *Cancer Treat Rev*. 2021;97:102205. doi:10.1016/j.ctrv.2021.102205.
12. Desmedt C, Salgado R, Fornili M, et al. Immune infiltration in invasive lobular breast cancer. *J Natl Cancer Inst*. 2018;110(7):768-776. doi:10.1093/jnci/djx268.
13. Tille JC, Vieira AF, Saint-Martin C, et al. Tumor-infiltrating lymphocytes are associated with poor prognosis in invasive lobular breast carcinoma. *Mod Pathol*. 2020;33(11):2198-2207. doi:10.1038/s41379-020-0561-9.
14. Ciriello G, Gatza ML, Beck AH, et al; for the TCGA Research Network. Comprehensive molecular portraits of invasive lobular breast cancer. *Cell*. 2015;163(2):506-519. doi:10.1016/j.cell.2015.09.033.
15. Michaut M, Chin SF, Majewski I, et al. Integration of genomic, transcriptomic and proteomic data identifies two biologically distinct subtypes of invasive lobular breast cancer. *Sci Rep*. 2016;6:18517. doi:10.1038/srep18517.
16. Du T, Zhu L, Levine KM, et al. Invasive lobular and ductal breast carcinoma differ in immune response, protein translation efficiency and metabolism. *Sci Rep*. 2018;8(1):7205. doi:10.1038/s41598-018-25357-0.