Into the twilight zone – should ER-low breast cancer be treated as triple negative breast cancer?

Helena Jernström[a,b,*] and Lisa Rydén[b,c]

[a]Department of Clinical Sciences Lund, Oncology, Lund University, Lund, Sweden
[b]Lund University Cancer Centre (LUCC) and Skåne University Hospital Comprehensive Cancer Center (SUHCC), Sweden
[c]Department of Clinical Sciences Lund, Surgery, Lund University and Skåne University Hospital, Lund, Sweden

The Lancet Regional Health - Europe 2024;40: 100896
Published Online xxx
https://doi.org/10.1016/j.lanepe.2024.100896

To date, there is no international standardization of therapeutic adjuvant guidelines for patients with ER-low breast cancer. According to most international guidelines, patients with ER-low tumours are recommended endocrine therapy, although there are conflicting results regarding the clinical benefit.[1] Including patients with ER-low HER2-negative tumours in the ER-positive subset makes them ineligible for treatments aimed at triple-negative breast cancer (TNBC). There are still substantial knowledge gaps based on real world data regarding the outcome for patients with ER-low tumours when treated as TNBC.

In this issue of the *Lancet Regional Health—Europe*, Ács et al. examined the overall survival and characteristics of patients with ER-zero and ER-low HER2-negative breast cancer when treated as TNBC in a large real world nationwide Swedish population-based cohort based on registry data.[2] Data for 5655 patients with ER-zero or ER-low HER2-negative primary breast cancer diagnosed 2008–2020 were presented. The median follow-up was 4.4 years and overall survival was selected as primary endpoint because virtually all deaths were due to breast cancer. The authors conclude that ER-low HER2-negative breast cancer should be treated as TNBC in order to enable these patients to receive adjuvant treatments aimed at TNBC.

After the cut-off for ER-positivity was changed from 10% to 1% in 2010,[3] Sweden retained the 10% cut-off for ER-positivity. Among patients with HER2-negative tumours, about 10% of ER-negative tumours in Sweden are ER-low.[2] These patients are thus treated as patients with TNBC and only rarely prescribed endocrine therapy.[2] Outside Sweden, the rates of adjuvant endocrine therapy for ER-low patients are also relatively low, which is likely due to the collective lack of substantiative evidence of endocrine therapy benefit in ER-low disease in combination with the well-known negative impact on quality of life.[4]

TNBC is a highly heterogenous subgroup of breast cancer.[5] In the study by Ács et al., there were some differences in tumour characteristics between patients with ER-zero and ER-low breast cancer, most notably that ER-zero tumours were associated with significantly higher frequency of Grade III and higher Ki67 as well as lower frequency of non-amplified HER2 2+ and lobular histopathology. In spite of these differences, the pathological complete response (pCR) rates were very similar between neoadjuvant treated patients with ER-low and ER-zero tumours. The association between achieving a pCR and overall survival was also similar. Among chemotherapy-treated patients, there was also no difference in overall survival. Moreover, in all patients, the overall survival did not differ significantly between patients with ER-zero and ER-low tumours whether or not the subset of patients who had received endocrine treatment was included in the analysis.

Normally, patients with node-negative TNBC <5 mm are not recommended chemotherapy in Sweden. Unfortunately, the authors presented tumour sizes as 1–20 mm and did not provide tumour size or nodal status separately in the full multivariable model. A full model could potentially have been used to identify prognostic factors to better select the subgroup of patients with ER-low tumours for whom chemotherapy could be omitted. Nonetheless, the findings are in line with another large real-world study from the US, where patients with low ER levels (even up to <20%) had poor clinical outcomes comparable to patients with TNBC.[6]

In this study, the overall survival for chemonaïve patients was significantly longer for those with ER-low tumours compared with ER-zero tumours.[2] Whether this difference also remained when patients with endocrine therapy were excluded was not reported. To date, there is no international standardization of therapeutic guidelines for ER-low breast cancer and studies have reported conflicting results regarding the benefit of endocrine treatment.[1] Molecular subtyping may be necessary in order to identify ER-low patients with the highest chance of responding to endocrine therapy since it is expected that at least a subgroup of ER-low cancers responds to endocrine therapy. The therapeutic response in this subgroup of patients differs according to the molecular basal or luminal subtype.[7]

Immune therapy is now approved for TNBC and would be a treatment option for a larger group of patients if patients with ER-low tumours were classified as TNBC. Whether the response to immunotherapy is

DOI of original article: https://doi.org/10.1016/j.lanepe.2024.100886
*Corresponding author. Department of Clinical Sciences Lund, Oncology, Lund University, Barngatan 4, SE-221 85, Lund, Sweden.
E-mail address: Helena.Jernstrom@med.lu.se (H. Jernström).

similar in patients with ER-low and ER-zero tumours was not reported in the study since immunotherapy was not yet approved for TNBC by the EMA. However, it is likely that patients with ER-low tumours would benefit from immunotherapy since the immune landscape of ER-low tumours mimic that of primary TNBC.[8] In the I-SPY2 and KEYNOTE-522 trials, immunotherapy significantly increased pCR rates in TNBC.[9,10]

Taken together, these data suggest that treating ER-low as TNBC may be beneficial for many breast cancer patients with ER-low disease. Molecular profiling may help identifying the subset of patients with ER-low tumours with the largest chance of endocrine treatment response. Including ER-low tumours in the group of TNBC would also allow these patients into trials with new drugs such as antibody drug conjugates.

Contributors

Helena Jernström drafted the first version of this commentary. Lisa Rydén provided critical feedback on the draft and both authors approved the final version of this commentary.

Declaration of interests

Helena Jernström and Lisa Rydén declare no conflict of interest.

References

1 Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. *J Clin Oncol*. 2020;38(12):1346–1366.

2 Ács B, Hartman J, Sönmez D, Lindman H, Johansson ALV, Fredriksson I. Real-world overall survival and characterstics of patients with ER-zero and ER-low HER2-negative breast cancer treated as triple-negative breast cancer: a Swedish population-based cohort study. *Lancet Reg Health Europe*. 2024. https://doi.org/10.1016/j.lanepe.2024.100886.

3 Hammond ME, Hayes DF, Dowsett M, et al. American society of clinical oncology/College of American pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol*. 2010;28(16):2784–2795.

4 Yoder R, Kimler BF, Staley JM, et al. Impact of low versus negative estrogen/progesterone receptor status on clinico-pathologic characteristics and survival outcomes in HER2-negative breast cancer. *NPJ Breast Cancer*. 2022;8(1):80.

5 Lehmann BD, Jovanovic B, Chen X, et al. Refinement of triple-negative breast cancer molecular subtypes: implications for neoadjuvant chemotherapy selection. *PLoS One*. 2016;11(6):e0157368.

6 Bari S, Boulware D, Li J, et al. A real-world data retrospective cohort study of low estrogen receptor-positive early breast cancer: natural history and treatment outcomes. *Breast Cancer (Dove Med Press)*. 2022;14:199–210.

7 Bertucci F, Finetti P, Goncalves A, Birnbaum D. The therapeutic response of ER+/HER2- breast cancers differs according to the molecular basal or luminal subtype. *NPJ Breast Cancer*. 2020;6:8.

8 Voorwerk L, Sanders J, Keusters MS, et al. Immune landscape of breast tumors with low and intermediate estrogen receptor expression. *NPJ Breast Cancer*. 2023;9(1):39.

9 Nanda R, Liu MC, Yau C, et al. Effect of pembrolizumab plus neoadjuvant chemotherapy on pathologic complete response in women with early-stage breast cancer: an analysis of the ongoing phase 2 adaptively randomized I-SPY2 trial. *JAMA Oncol*. 2020;6(5):676–684.

10 Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for early triple-negative breast cancer. *N Engl J Med*. 2020;382(9):810–821.