The mystery of ER-negative/PR-positive breast cancer: revisiting the endocrine therapy controversy using national data

Shawn M. Doss, BA; Priyanka Raval, MD
Department of Medicine, Medical College of Georgia, Augusta, GA

INTRODUCTION

- Breast cancer classification by hormone receptor (HR) status critically guides therapy and prognosis.
- HR-discordant tumors (ER-/PR+) present therapeutic dilemmas, as endocrine therapy is guided by ER status.
- ER-/PR+ tumors account for less than 1% of all invasive breast cancers, yet clinical management remains inconsistent (typically treated as triple-negative).

Biologic Ambiguity:

❖ Some hypothesize PR+ with ER- is due to technical staining variability or assay sensitivity issues.
❖ Others propose molecular heterogeneity with retained PR expression through non-estrogen pathways.

Clinical Challenges:

❖ Guidelines recommend endocrine therapy (ET) for ER+ disease rather than for any positive HR status.
❖ However, could ET in ER-/PR+ improve survival if even partial hormone responsiveness exists?

- Prior evidence (pre-2015) has largely dismissed ET benefit in this ER-/PR+ group.
- Recent analyses, including genomic subtyping, suggest subsets of ER-/PR+ tumors may share features with luminal cancers, possibly explaining improved outcomes with ET in these cases.

- **This study seeks to clarify the role of ET in ER-/PR+ early-stage disease treated with chemotherapy using real-world national registry data to reflect modern practice patterns.**

METHODS AND MATERIALS

- **Data Source:** National Cancer Database, 2010–2020.
- **Population:** Women ≥40 years at diagnosis, stage I–III, ER-/PR+, treated with chemotherapy.
- **Exclusions:** Stage IV disease, incomplete receptor or survival data.
- **Covariates:** Age, race/ethnicity, HER2, grade, stage, facility type, and zip code median income.

Analyses:

- Multivariate logistic regression for factors associated with ET omission.
- Multivariate Cox regression for 3-year overall survival (OS) (hazard of mortality over 3 years, versus ET omission).
- Stratified by 2010–2017 vs. 2018–2020 to capture prognostic staging updates and NCDB coding changes.

Sensitivity tests:

- HER2-negative subgroup analysis.
- Landmark analysis (≥6 months survivors).
- Propensity score matched analysis (by above covariates).

Table 1. Summarized Results of Cox Regression Models for Three-Year OS

Analysis Type	2010–2017 (aHR, 95% CI)	p-value	2018–2020 (aHR, 95% CI)	p-value
Multivariable Cox	0.54 (0.47–0.62)	<0.001	0.60 (0.48–0.77)	<0.001
HER2-negative subset	0.59 (0.50–0.69)	<0.001	0.63 (0.48–0.81)	<0.001
Landmark (≥6 months survival)	0.60 (0.52–0.70)	<0.001	0.70 (0.55–0.89)	0.004
Propensity Score Matched	0.57 (0.49–0.66)	<0.001	0.66 (0.50–0.87)	0.003

RESULTS

Cohort Summary:

- 24,198 ER-/PR+ cases (0.94% of all breast cancer cases).
- Of these, 18,788 (77.6%) were stage I–III at diagnosis.
- Of these, 13,957 (74.3%) received chemotherapy.
- 11,558 patients met inclusion with complete covariates.

Demographics:

- Median age: 57 years (IQR 48–65).
- Race/ethnicity: 68% White, 22% Black, 10% Other.
- 60.2% HER2-negative; 75.1% high grade.
- Stage I: 38.5%, Stage II: 43.5%, Stage III: 18.0%.

Endocrine Therapy Use:

- ET omitted in 33.8% of ER-/PR+ patients in final cohort.
- Median age of ET omission: 58 vs. 57 among ET recipients.

Predictors of ET Omission (Logistic Regression):

- Diagnosis in 2018–2020 vs 2010–2017: aOR 1.95 (95% CI 1.75–2.17, p<0.001).
- Age 70–80 vs. 40–50: aOR 1.34 (95% CI 1.16–1.55, p<0.001).
- High-grade tumor: aOR 1.15 (95% CI 1.03–1.28, p=0.02).
- No significant association for stage, HER2 status, or facility type.

Overall Survival (Cox Regression):

- ET associated with improved three-year OS (decreased hazard of mortality) in both eras (See **Table 1**).
- Interaction term for period non-significant (p=0.59).

DISCUSSION

- ET improved OS in chemotherapy-treated stage I–III ER-/PR+ breast cancer.
- Findings persisted after controlling for confounders, staging changes, and propensity score matching.

Possible Explanations

- PR expression may indicate residual hormone signaling despite negative ER testing.
- Some ER-/PR+ tumors may be “ER-low” or possess partial receptor cross-talk.
- ER/PR discordance can result from assay variability, cut-off thresholds, or tissue fixation issues.

Limitations:

- Retrospective design cannot establish causality; lack of recurrence and disease-specific survival data.
- No central receptor re-evaluation or molecular profiling.

Strengths:

- Largest real-world national dataset examining ET outcomes in this rare subtype.
- Inclusion of validation analyses to increase robustness.

CONCLUSIONS

- Omission of ET in ER-/PR+ early-stage breast cancer treated with chemotherapy was linked to worse survival.
- The ET survival benefit persisted after matching and stratification, regardless of HER2 status.
- Updated prospective studies and standardized receptor testing are needed to guide treatment recommendations.

Contact
Shawn Doss
Medical College of Georgia
shdoss@augusta.edu

This presentation is the intellectual property of the author/presenter. Contact them at shdoss@augusta.edu for permission to reprint and/or distribute.

References

1. Hefti MM, Hu R, Knoblauch NW, et al. Estrogen receptor negative/progesterone receptor positive breast cancer is not a reproducible subtype. *Breast Cancer Res*. 2013;15(4):R68. doi:10.1186/bcr3462
2. Rakha EA, El-Sayed ME, Green AR, et al. Biologic and Clinical Characteristics of Breast Cancer With Single Hormone Receptor–Positive Phenotype. *JCO*. 2007;25(30):4772-4778. doi:10.1200/JCO.2007.12.2747
3. Yang LH, Tseng HS, Lin C, et al. Survival Benefit of Tamoxifen in Estrogen Receptor-Negative and Progesterone Receptor-Positive Low Grade Breast Cancer Patients. *Journal of Breast Cancer*. 2012;15(3):288-295. doi:10.4048/jbc.2012.15.3.288
4. Kollu V, Osterloth K, Borgert AJ, Frankki SM, Parsons BM. Impact of endocrine therapy on overall survival in ER negative/PR positive locoregional breast cancer: An analysis of the National Cancer Database. *JCO*. 2021;39(15_suppl):545-545. doi:10.1200/JCO.2021.39.15_suppl.545