# Association between Event-free/Distant Relapse-free Survival and Overall Survival in Patients with Early-Stage Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative (ER+/HER2-) Breast Cancer

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## Background

- While overall survival (OS) is a universally accepted measure of clinical benefit, prolonged follow-up is needed to observe sufficient events, especially in diseases such as early breast cancer (BC) where life expectancy has significantly increased due to better treatments. Establishing validated surrogate endpoints for OS can support early evaluation of treatment efficacy to help inform accelerated regulatory and reimbursement approval
- Gogate, et al 2023 concluded from trial-level associations that event-free survival (EFS) or disease-free survival (DFS) endpoints are appropriate surrogates for OS in a broad HR+/HER2- BC setting[1]
- Recently, new treatment options have focused on patients at high risk of recurrence.[2,3] In this study, we attempted to assess surrogacy in patients with early-stage, high-risk HR+/HER2- BC population receiving neoadjuvant followed by adjuvant (perioperative) therapy. Specifically, the evaluation of distant relapse-free survival (DRFS) or EFS as surrogates for OS among this early stage, high-risk population has yet to be established

## Objective

- To evaluate the surrogate relationship between EFS, DRFS or comparable endpoints, related with OS, among patients with high-risk, early-stage HR+ or ER+/HER2- BC receiving neoadjuvant/adjuvant therapy

## Methods

### Methods for systematic literature review

- The systematic literature review (SLR) was conducted following the PRISMA guidelines[4] with searches conducted in MEDLINE®, Embase®, MEDLINE in-Process and the Cochrane Library (search date - December 4, 2023) and the Population, Intervention, Comparator, Outcome, and Study design (PICOS) are listed in **Table 1**
- Included studies reported endpoints comparable to established definitions for EFS and DRFS
  - EFS was defined as the time from randomization to disease progression precluding surgery, local or distant recurrence, second primary malignancy or death due to any cause, whichever occurs first
  - DRFS was defined as the time from surgery to distant recurrence as assessed by investigator, or death from any cause, whichever occurred first

**Table 1. PICOS criteria for review**

| | |
|---|---|
| **Population** | Adult patients with early-stage HR+ or ER+/HER2- breast cancer[a] |
| **Intervention** | Chemotherapy in the neoadjuvant setting with adjuvant endocrine therapy ± adjuvant chemotherapy |
| **Comparator** | • Chemotherapy in the neoadjuvant setting with adjuvant endocrine therapy ± adjuvant chemotherapy<br>• No neoadjuvant therapy with adjuvant endocrine ± adjuvant chemotherapy<br>• Adjuvant endocrine therapy use required for non-comparative studies |
| **Outcomes[b]** | EFS, DRFS, DDFS, DFS, RFS (if comparable), OS |
| **Study design** | RCT, non-randomized comparative studies, single-arm trials, prospective or retrospective observational studies, systematic reviews, meta-analyses, or NMAs of clinical trials[c] |

Key: DDFS, distant disease-free survival; DRFS, distant recurrence-free survival; EFS, event-free survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NMA, network meta-analysis; OS, overall survival; RCT, randomized controlled trials; RFS, recurrence-free survival; SLR, systematic literature review.

Notes: [a]Due to scarce evidence for high-risk patient study populations, requirements were relaxed; among HR+ patients, the vast majority (>90%) are estrogen receptor positive (ER+) (Chan 2015).[5]

[b]Definitions for EFS or DRFS were reported in the comparator trials also as DFS, DRFS, DDFS, or RFS and thus these comparable outcomes were captured as their definition aligned with the predefined definitions of EFS or DRFS.

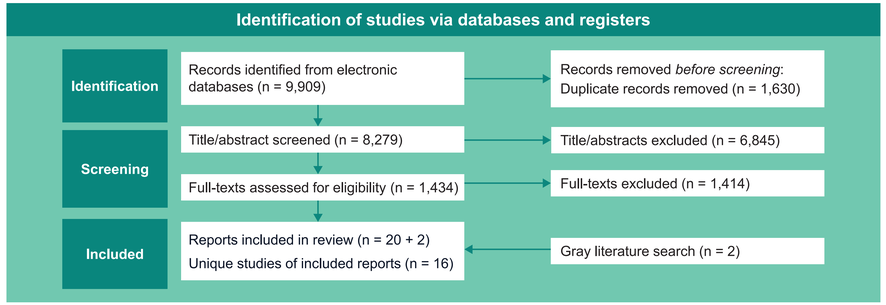
[c]For reference cross-checking only.

### Methods for surrogate outcome analyses

- Trial-level and arm-level evidence was considered, based on published hazard ratios or landmark survival rates (reported or digitized from Kaplan-Meier curves), respectively
- Association between the relevant surrogacy endpoints and OS was estimated using unweighted, sample weighted, and inverse variance weighted linear regression models:
  - Primary analysis of logistics hazard ratios between surrogacy endpoints and OS; landmark 3-year surrogacy endpoints with 5-year OS
  - Secondary analyses of 3-year surrogacy endpoints with 3-year OS, and 5-year surrogacy endpoints with 5-year OS
- Strength of association between surrogacy endpoints and OS was quantified using the coefficient of determination ($R^2$), and Pearson and Spearman's correlation coefficients ($\rho$), with bootstrapped 95% confidence intervals (CIs). Both correlation methods were included due to the small sample size of included studies, making normality assumptions difficult to assess
- Though there is no universally agreed upon threshold, following categorization used in other surrogacy assessments[6], strength of correlation was defined as high for $\rho \geq 0.85$, moderate for $\rho > 0.7$ to $\rho < 0.85$, and low for $\rho \leq 0$

## Results

**Figure 1. PRISMA diagram**




- A lack of evidence was found for high-risk HR+/HER2- BC, thus the broader study population was considered for analysis. Even when relaxing high-risk criteria, the evidence base was very small
  - From 9,909 records (**Figure 1**), the SLR identified 16 unique studies. 15 studies reported DRFS or potentially equivalent endpoints (DFS, DDFS, and RFS) and only one study reported EFS (Dredze 2022), thus assessment of EFS as a surrogate endpoint was deemed unfeasible
  - Notably, none of the resulting studies specified the study population to be high risk HR+/HER2-
  - When reported, HR+/ER+ status varied between studies, with positive cell cutoffs ranging from ≥1% to >10%
- All studies but two (Yang 2023, van Hellemond 2020) were single cohort studies, thus trial-level surrogacy analysis requiring hazard ratios was not feasible
- Due to substantial differences in reporting with respect to the established definition of DRFS, four studies were excluded from the surrogacy analysis (**Table 2**)
- Among the 11 studies reporting DRFS (or comparable endpoints), three studies were excluded from the base case and only entered scenario analyses due to their lack of clarity whether death was included in the definition. DRFS or comparable endpoint definitions included DFS
- One study (Zhang 2023) only reported 3-year endpoints, thus did not contribute to 5-year assessments
- The 10 studies with 5-year endpoint data reported a median follow-up time of 8.4 years for DRFS (or comparable endpoint) and 9.4 years for OS

**Table 2. Studies considered for inclusion in surrogate outcome analysis**

| Study | HER2-subpopulation | Intervention | Sample size | Surrogate endpoint | Data available (3- and 5-yr) | Analysis inclusion |
|---|---|---|---|---|---|---|
| Studies reporting DRFS or potentially equivalent endpoints | | | | | | |
| Angelucci 2013[7] | HR+ | NAC + adj ET | 211 | DRFS | Arm-level | BC,S |
| Chen 2023[8] | ER+ | MR (>80% CT) + adj ET | 159 | DFS | Arm-level | BC,S |
| Hayashi 2020[9] | ER+ | NAC + adj TAM or AI | 38 | DFS | Arm-level | BC,S |
| Luangdilok 2014[10] | HR+ | MR + adj ET (+/- CT) | 107 | DFS | Arm-level | BC,S |
| Krishnan 2013[11] | HR+ | NAC + adj TAM or AI | 162 | DFS | Arm-level | BC |
| Yang 2023[12] | HR+ | NAC + adj ET + CT | 379 | DDFS | Study and arm-level | N |
| Zhang 2013[13] | HR+ | NAC + adj ET | 145 | DFS | Arm-level | BC,S |
| Zhang 2024[14] | HR+ | NAC + adj TAM or AI | 239 | DFS | Arm-level | BC |
| Zhang 2023[15] | HR+ | NAC + adj AI + SERMs | 3,070 | DFS | Arm-level[a] | BC |
| Miglietta 2020[16] | ER+ | NAC + adj ET | 105 | DFS | Arm-level | BC,S |
| van Hellemond 2020[17] | ER+ | NAC + adj Anastrozole | 656 | DRFS | Arm-level | BC,S |
| Grassadonia 2021[18] | HR+ | NAC + adj ET | 168 | DFS | Arm-level | N |
| Marta 2020[19] | HR+ | NAC + adj ET | 478 | DFS | Arm-level | BC,S |
| Aksoy 2020[20] | HR+ | NAC + adj ET | 73 | DFS | Arm-level | N |
| Kuhar 2023[21] | HR+ | NAC + adj ET | 88 | RFS | Arm-level | N |
| Studies reporting EFS or equivalent endpoints | | | | | | |
| Dredze 2022[22] | HR+ | D-C then paclitaxel+ adj TAM or AI | 105 | EFS | Arm-level | N |

Key: Adj, adjuvant; AIs, aromatase inhibitors; BC, base case; CT, chemotherapy; D-C, doxorubicin-cyclophosphamide; DDFS, distant disease-free survival; DRFS, distant recurrence-free survival; EFS, event-free survival; ET, endocrine therapy; HR, hazard ratio; MR, magnetic resonance; N, not included for any analysis; NAC, neoadjuvant chemotherapy; RCT, randomized controlled trial; RFS, relapse-free survival; S, scenario; SERMs, selective estrogen receptor modulators; TAM, tamoxifen; yr, year.

Note: [a]Only 3-yr arm-level data is available; gray rows indicate studies excluded from analysis due to lack of comparable endpoint data.

- Regardless of weighting method, moderate to high correlations were found between DRFS and OS for all timepoints (**Table 3**). Associated 95% CIs were found to be wide, due to the small number of studies and limited sample size in most studies
- Correlation estimates were higher in the scenario analysis, which excludes the study with the largest population (Zhang 2023), compared to the base case analysis

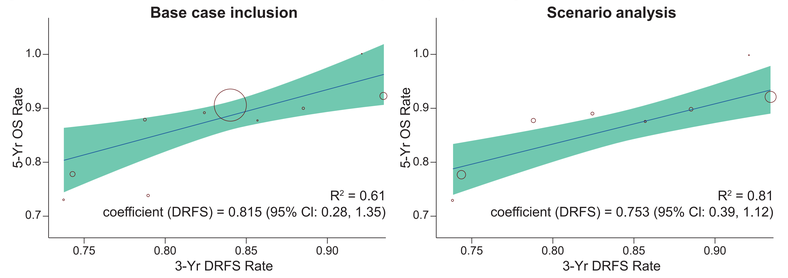
**Table 3. Summary of arm-level correlations for surrogacy associations**

| Surrogacy assessment | Analysis | Model type | $R^2$ (95% CI) | Pearson (95% CI) | Spearman (95% CI) |
|---|---|---|---|---|---|
| 3-year DRFS/5-year OS | **Base case** | **Sample weighted** | **0.61 (0.32, 0.92)** | **0.78 (0.56, 0.96)** | **0.80 (0.25, 1.00)** |
| | Base case | Inverse variance weighted | 0.54 (0.33, 0.91) | 0.74 (0.57, 0.96) | 0.86 (0.16, 1.00) |
| | Base case | Unweighted | 0.72 (0.435, 0.92) | 0.85 (0.66, 0.96) | 0.84 (0.43, 1.00) |
| | **Scenario** | **Sample weighted** | **0.81 (0.45, 0.97)** | **0.90 (0.67, 0.99)** | **0.97 (0.64, 1.00)** |
| 3-year DRFS/3-year OS | Base case | Sample weighted | 0.78 (0.38, 0.96) | 0.89 (0.62, 0.98) | 0.72 (0.13, 1.00) |
| 5-year DRFS/5-year OS | Base case | Sample weighted | 0.79 (0.52, 0.94) | 0.89 (0.72, 0.97) | 0.99 (0.68, 1.00) |

Key: CI, confidence interval; DRFS, distant recurrence-free survival; OS; overall survival.

Note: Green values indicate measures of strong correlation; yellow values indicate measures of moderate correlation; bolded rows indicate models which are presented graphically.

**Figure 2. Arm-level associations for 3-yr DRFS and 5-yr OS (sample weighted)**




## Conclusions

- Limited evidence on EFS or DRFS reported with OS for high-risk, early stage HR+/HER2- BC in neoadjuvant/adjuvant settings makes it difficult to estimate the surrogacy relationships
- No publications were found specifically on the high-risk subpopulation
- Though endpoint definitions from studies included in the DRFS and OS arm-level correlation assessments were deemed comparable, the lack of consistency in surrogate endpoint definitions is a limitation
- Lack of randomized control trials (RCTs) prevents the evaluation of surrogacy relationships to support Level 1[23] (most robust) evidence (which requires relative treatment effects from RCTs)
- Our analysis of treatment-arm landmark survival rates suggests DRFS (and identified comparable endpoints) as a potential surrogate for OS in the HR+ HER2- BC landscape, despite the small number of studies available. Future RCTs in this specific disease population could provide further insights to inform current surrogacy estimation findings

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Presented at ISPOR; Montreal, Canada; May 13-16, 2025.