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Prognostic Impact of Pathological Complete Response in Hormone Receptor–Positive/HER2-Negative Breast Cancer Treated with Neoadjuvant Chemotherapy: A Multicenter Cohort Study

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Running Title: pCR and Survival in HR-Positive/HER2-Negative Breast Cancer

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Abstract

Background:
Pathological complete response (pCR) is an established surrogate endpoint in aggressive breast cancer subtypes; however, its prognostic role in hormone receptor (HR)-positive/HER2-negative disease remains controversial. We aimed to evaluate clinicopathological predictors of pCR and to investigate the prognostic impact of pCR on event-free survival (EFS) and overall survival (OS) in HR-positive/HER2-negative breast cancer treated with neoadjuvant chemotherapy (NAC).

Methods:
This multicenter retrospective cohort study included 379 patients with HR-positive/HER2-negative breast cancer treated with NAC between 2010 and 2025. ER and PR expression levels, Ki-67 index, and histopathological features were analyzed. Factors associated with pCR were evaluated using Firth penalized logistic regression. Survival outcomes were assessed using Kaplan–Meier analysis and Cox proportional hazards models**.**

Results:
pCR was achieved in 18.7% of patients. Lower ER expression (≤10%) and higher Ki-67 (≥20%) were independently associated with increased likelihood of achieving pCR. In multivariate analysis, ER expression >10% was associated with significantly lower odds of pCR, whereas Ki-67 ≥20% independently increased the probability of pCR.

Achieving pCR was independently associated with improved EFS (HR range, 0.13–0.17 across models). Younger age and high Ki-67 were also independently associated with worse EFS, while lymphovascular invasion (LVI) retained prognostic significance in one multivariable model.

In contrast, pCR was not independently associated with OS. Higher ER expression was consistently associated with improved OS, while advanced nodal disease (pN3) emerged as the strongest independent predictor of worse OS.

Conclusions:
In HR-positive/HER2-negative breast cancer, pCR remains an uncommon outcome and is primarily associated with lower ER expression and higher proliferative activity. Although achieving pCR was independently associated with improved EFS, it did not independently predict OS within the current follow-up period. These findings suggest that pCR may be a useful surrogate endpoint for recurrence-related outcomes but should be interpreted cautiously as a marker of long-term survival in this subgroup. Quantitative assessment of ER expression and Ki-67 may help identify patients more likely to benefit from NAC. Further prospective studies with longer follow-up and external validation are warranted.

Keywords: Hormone receptor-positive breast cancer; HER2-negative; neoadjuvant chemotherapy; pathological complete response; Ki-67; estrogen receptor; event-free survival

Introduction

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Neoadjuvant chemotherapy (NAC) has become an established treatment strategy for locally advanced and inoperable breast cancer and is increasingly being adopted for operable tumors to improve surgical outcomes and enable breast-conserving surgery (BCS) [1,2]. Beyond tumor downstaging, NAC provides a unique opportunity to assess in vivo tumor sensitivity to systemic therapy and to identify early surrogate markers of long-term outcomes. Pathological complete response (pCR), defined as the absence of residual invasive disease in the breast and axillary lymph nodes, has emerged as an important endpoint in the neoadjuvant setting [2,3].

Large pooled analyses have demonstrated that pCR is strongly associated with improved event-free survival (EFS) and overall survival (OS), particularly in biologically aggressive subtypes such as triple-negative and HER2-positive breast cancer [3,4]. However, this relationship appears substantially weaker in hormone receptor (HR)-positive/HER2-negative tumors, which not only achieve significantly lower pCR rates but also derive most of their systemic benefit from adjuvant endocrine therapy rather than chemotherapy [3–7]. In HR-positive disease, pCR has been more consistently associated with improved EFS, whereas its correlation with OS remains less clear and less robust compared to other intrinsic subtypes [4,5].

HR-positive/HER2-negative breast cancer represents the most common molecular subtype and is characterized by distinct biological behavior. Luminal tumors, particularly those classified as luminal A, are typically less proliferative, more hormonally driven, and relatively less chemosensitive. In contrast, tumors with higher proliferative activity, often categorized as luminal B subtype, demonstrate greater sensitivity to cytotoxic therapy [8,9]. Accordingly, reported pCR rates in HR-positive/HER2-negative breast cancer generally range between 5% and 18% following NAC, reflecting the limited chemosensitivity of this subgroup [2,10].

The role of NAC in HR-positive/HER2-negative breast cancer remains controversial. Despite relatively low pCR rates compared with triple-negative and HER2-positive disease, NAC may still facilitate breast-conserving surgery and improve local treatment options in selected patients. Conversely, neoadjuvant endocrine therapy (NET) has emerged as an alternative strategy for strongly hormone receptor-positive, low-proliferative tumors, particularly among postmenopausal women. Consequently, identifying biomarkers that can predict response to NAC is of considerable clinical importance and may help optimize treatment selection while minimizing unnecessary toxicity [11,12,13].

Although proliferative markers and intrinsic subtype classification have been linked to chemotherapy response, the independent role of quantitative estrogen receptor (ER) and progesterone receptor (PR) expression levels in predicting pCR in HR-positive/HER2-negative breast cancer remains unclear [8,9,14]. Furthermore, the prognostic implications of achieving pCR in this subgroup, particularly with respect to EFS and OS, are not fully established [2,4].

Therefore, in the present study, we aimed to investigate the clinicopathological predictors of pCR and to evaluate its prognostic significance for both EFS and OS in patients with HR-positive/HER2-negative breast cancer treated with NAC. Unlike previous studies focusing primarily on pCR rates or survival outcomes alone, our study simultaneously examines quantitative hormone receptor expression, proliferative activity, predictors of pCR, and their

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independent associations with both recurrence-related and overall survival outcomes in a multicenter real-world cohort.

Materials and Methods

Study Design and Patient Population

This multicenter retrospective cohort study included patients diagnosed with HR-positive/HER2-negative breast cancer who were treated with NAC between January 2010 and January 2025 at three tertiary oncology centers: Antalya Training and Research Hospital (Antalya), Karadeniz Technical University (Trabzon), and Adıyaman Training and Research Hospital (Adıyaman), Turkey. A total of 379 consecutive patients were identified from institutional databases.

Eligibility criteria included: (1) histologically confirmed invasive breast carcinoma; (2) ER-positive and/or PR-positive disease; (3) HER2-negative status defined as IHC 0–1+, or IHC 2+ with negative FISH according to ASCO/CAP guidelines; (4) treatment with standard NAC followed by definitive breast and axillary surgery; and (5) availability of clinicopathological and follow-up data. Patients with metastatic disease at diagnosis or incomplete pathological data were excluded. Among the 379 included patients, five (1.3%) had an ER-negative/PR-positive phenotype; the remaining patients were ER-positive.

Patients were treated according to institutional standards during the study period, predominantly consisting of sequential anthracycline- and taxane-based NAC regimens. Indications for NAC included tumor downstaging to facilitate BCS, locally advanced disease, clinically node-positive disease, large tumor size relative to breast volume, and biologically aggressive tumor characteristics according to institutional practice and treating physician discretion.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Adıyaman University Ethics Committee (Approval No: 2025/10-2; Date: December 16, 2025). Institutional approvals were also obtained from the participating centers, including Antalya Training and Research Hospital and Karadeniz Technical University. Due to the retrospective design of the study, the requirement for informed consent was waived.

Pathological Data Collection and Definitions

Clinicopathological data were retrospectively extracted from institutional pathology reports and electronic medical records. Collected variables included histological subtype, tumor grade, clinical T and N stage at diagnosis, type of surgery performed, lymphovascular invasion (LVI), perineural invasion (PNI), pathological tumor (pT) and nodal (pN) stage following NAC, pCR status, and regression score.

Information on adjuvant treatments, including ovarian suppression with LHRH analogs and endocrine therapy, was also recorded. In routine clinical practice, ovarian suppression with LHRH analogs was generally administered to selected premenopausal patients according to contemporary treatment guidelines and physician discretion, considering factors such as age, menopausal status, recurrence risk, and planned endocrine therapy.

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For analytical purposes, ER expression was categorized as ≤10%, 10–40%, and >40%. The ≤10% threshold was selected based on the established ER-low category and its reported association with distinct biological behavior and reduced endocrine responsiveness [15,16]. Because no universally accepted cutoff exists for distinguishing intermediate from strongly ER-positive tumors, the >40% category was used for exploratory stratification and to evaluate potential differences in treatment response and survival outcomes across increasing levels of ER expression. Ki-67 was categorized as <20% and ≥20%, consistent with commonly used thresholds for distinguishing low- and high-proliferative luminal tumors [17]. PR expression was dichotomized at 50% for exploratory analyses. Although lower thresholds such as 10% and 20% have been reported in previous studies, no universally accepted PR cutoff exists for predicting response to NAC in HR-positive/HER2-negative breast cancer. Therefore, the 50% threshold was selected to provide balanced subgroup sizes and reduce estimation instability related to small subgroup frequencies [16,18]. While this threshold provided a clinically interpretable classification of PR expression, it may be dataset-specific and requires validation in independent cohorts.

Given the retrospective nature of the study, some clinicopathological variables were missing in a subset of patients. Statistical analyses were conducted based on available data for each parameter.

Definition of Pathological Complete Response

pCR was defined as the absence of residual invasive carcinoma in both the breast and axillary lymph nodes following NAC (ypT0/is ypN0). Residual disease was staged according to the AJCC staging system.

Follow-up and Outcome Measures

EFS was defined as the time from diagnosis to the first occurrence of disease progression (local, regional, contralateral breast cancer, or distant metastasis) or death from any cause, whichever occurred first.

OS was defined as the time from diagnosis to death from any cause.

Patients without an event were censored at the date of last follow-up.

Statistical Analysis

The normality of continuous variables was assessed using the Kolmogorov–Smirnov test (Lilliefors correction) when the sample size was ≥50 and the Shapiro–Wilk test when the sample size was <50. As most continuous variables did not demonstrate normal distribution, non-parametric tests were applied.

Comparisons between two independent groups were performed using the Mann–Whitney U test. For comparisons involving three or more groups, the Kruskal–Wallis H test was used. When the Kruskal–Wallis test indicated statistical significance, post hoc pairwise comparisons were conducted using Dunn's test with Bonferroni correction. For categorical variables,

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Fisher's exact test was applied due to small expected cell counts. Multiple comparisons of proportions were evaluated using the Bonferroni-adjusted Z test.

Factors associated with pCR were analyzed using Firth penalized logistic regression models to reduce small-sample bias and address potential issues of quasi-complete separation. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

EFS and OS were estimated using the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards regression models were used to identify factors independently associated with EFS and OS. Multivariable models were constructed to adjust for potential confounding clinicopathological variables. Candidate variables were selected based on clinical relevance and the results of univariable analyses. The number of variables included in each multivariable model was restricted according to the number of outcome events to reduce the risk of overfitting. Highly correlated variables were not included in the same model to minimize multicollinearity. HRs with 95% CIs were reported.

Continuous variables were summarized as mean ± standard deviation or median (minimum–maximum), as appropriate. Categorical variables were presented as frequencies (n) and percentages (%). A two-sided p-value <0.05 was considered statistically significant.

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA).

Results

Patient Characteristics

A total of 379 patients were included in the study. The mean age was 53.08 ± 11.51 years (median: 51, range: 28–87). More than half of the patients were pre/perimenopausal (55.1%), while 44.8% were postmenopausal. Most patients were diagnosed at advanced stages; 39.8% were stage 2B and 27.9% were stage 3A. Regarding clinical T classification, the majority were cT2 (64.4%). Most patients had nodal involvement at diagnosis, with cN1 observed in 58.8% of cases.

Invasive ductal carcinoma was the predominant histological subtype (92.3%). Most tumors were grade 2 (62%), followed by grade 3 (26.2%).

Hormone receptor analysis showed that 82% of patients had ER expression >40%, while 8.2% had ER ≤10%. PR expression was >50% in 53.1% of cases. Ki-67 ≥20% was observed in 71.5% of tumors.

BCS combined with either sentinel lymph node dissection (SLND) or axillary dissection (AD) was performed in 39.8% of patients, whereas modified radical mastectomy (MRM) with SLND or AD was performed in 60.2%, representing the most common surgical approach.

pCR was achieved in 71 patients (18.7%), whereas 308 patients (81.3%) had residual invasive disease. The distribution of pathological tumor stage showed that pT1 was the most common category (49.3%). Regarding nodal status, 40.1% of patients were classified as pN0, while 59.9% had residual nodal involvement (pN1–3).

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Regression score data were available for 361 patients, among whom partial response was the most frequent finding (41%), followed by near-complete or complete response (30.4%).

Information on LVI and PNI was available for a subset of patients and was reported according to available pathology records. LVI was observed in 40.4% and PNI in 18.7% of evaluable cases (Table 1).

Table 1. Baseline Demographic and Clinical Characteristics of the Patients

	n(%)/mean ± SD	Median(Min-Max)
Age	53.08 ± 11.51	51 (28 - 87)
Menopausal status		
Pre-perimenopausal	209	55.1
Post-menopausal	170	44.8
Clinical Stage		
2A	52	14
2B	147	39.8
3A	103	27.9
3B	32	8.6
3C	37	10
cT		
1	51	13.7
2	239	64.4
3	41	11.1
4	40	10.8
cN		
0	28	7.5
1	218	58.8
2	89	24
3	36	9.7
Histology		
Invasive ductal carcinoma	350	92.3
Invasive lobular carcinoma	20	5.2
Others	9	2.3
Grade		
1	44	11.9
2	230	62
3	97	26.2
ER		
≤10	31	8.2
10-40	37	9.8
>40	309	82
PR		
≤50	177	46.9
>50	200	53.1
HER2		

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0	211	55.6
1	81	21.3
2	87	22.9
Ki67		
<20	104	28.5
≥20	261	71.5
Surgery type		
BCS+SLND	67	17.6
MRM+AD	184	48.5
BCS+AD	84	22.1
Mastectomy/MRM+SLND	44	11.6
pCR		
No	308	81.3
Complete Response	71	18.7
pT		
0	76	20
1	183	49.3
2	98	25.8
3	16	4.2
4	6	1.5
pN		
0	152	40.1
1	136	35.8
2	65	17.1
3	26	6.8
LVI (n=307)		
Absent	183	59.6
Present	124	40.4
PNI (n=299)		
Absent	243	81.3
Present	56	18.7
Regression Score (n=361)		
No Response	47	13
Minimal Response	56	15.5
Partial Response	148	41
Near-complete Response	39	10.8
Complete Response	71	19.7

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Abbreviations: SD: Standard deviation; Min: Minimum; Max: Maximum; cT: Clinical tumor stage; cN: Clinical nodal stage; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; Ki-67: Proliferation index; BCS: Breast-conserving surgery; SLND: Sentinel lymph node dissection; AD: Axillary dissection; MRM: Modified radical mastectomy; pCR: Pathological complete response; pT: Pathological tumor stage; pN: Pathological nodal stage; LVI: Lymphovascular invasion; PNI: Perineural invasion.

Note: Percentages were calculated using the number of evaluable patients for each variable. The corresponding denominators are indicated within the table where missing data were present.

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Factors Associated with pCR

When pathological characteristics were compared between patients with and without pCR, several significant associations were identified (Table 2).

Median ER expression was significantly lower in the pCR group compared with the non-pCR group (80% vs. 90%, p=0.004). The probability of achieving pCR decreased markedly with increasing ER expression, with rates of 48.4% for ER ≤10%, 16.2% for ER 10–40%, and 15.1% for ER >40% (p<0.001).

Similarly, PR levels were significantly lower in the pCR group (median 30% vs. 60%, p=0.001). The pCR rate was significantly higher in tumors with PR ≤50% compared with those with PR >50% (23.3% vs. 13.7%, p=0.017).

Ki-67 was significantly higher among patients achieving pCR (median 40% vs. 25%, p<0.001). The pCR rate was significantly higher in tumors with Ki-67 ≥20% compared with those with Ki-67 <20% (24.3% vs. 6.9%, p<0.001).

No significant differences were observed for age, menopausal status, clinical T stage, clinical N stage, histological subtype, LVI, tumor grade, or HER2 IHC category (0/1+/2+), (all p>0.05).

Surgical approach differed significantly according to pCR status (p<0.001). BCS and SLND was more commonly performed among patients who achieved pCR (32.9% vs. 14.3%), whereas MRM and AD was more frequently performed among patients without pCR (53.9% vs. 25.7%).

Adjuvant GnRH analog use did not differ between groups (p=0.653). However, adjuvant hormonal therapy distribution differed between groups (p=0.038), with a higher proportion of patients without adjuvant therapy in the pCR group.

Table 2. Association Between Pathological Complete Response (pCR) and Clinicopathological Characteristics

	No pCR (n=308)	pCR (n=71)	p
Age	51.5 (28 - 87)	51 (33 - 73)	0.337[m]
Menopausal status			
Pre-perimenopausal	168 (54.5)	42 (59.2)	0.481[x]
Post-menopausal	140 (45.5)	29 (40.8)	
cT (n=366)			
1	42 (14.1)	9 (13)	
2	191 (64.3)	46 (66.7)	0.687[x]
3	34 (11.4)	5 (7.2)	
4	30 (10.1)	9 (13)	
cN (n=366)			
0	22 (7.4)	5 (7.2)	
1	175 (58.9)	40 (58)	0.983[f]
2	71 (23.9)	18 (26.1)	
3	29 (9.8)	6 (8.7)	
Histology (n=370)			

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Invasive ductal carcinoma	282 (94)	68 (97.1)	0.390[f]
Invasive lobular carcinoma	18 (6)	2 (2.9)	
LVI (n=304)			
Absent	163 (60.1)	20 (60.6)	0.959[x]
Present	108 (39.9)	13 (39.4)	
Grade (n=366)			
1	40 (13.5)	4 (5.8)	
2	186 (62.6)	41 (59.4)	0.068[x]
3	71 (23.9)	24 (34.8)	
ER	90 (0 - 100)	80 (0 - 100)	**0.004[m]**
ER (n=373)			
≤10	16 (5.2)[a]	15 (22.4)[b]	
10-40	31 (10.1)[a]	6 (9)[a]	**<0.001[f]**
>40	259 (84.6)[a]	46 (68.7)[b]	
PR	60 (0 - 100)	30 (0 - 100)	**0.001[m]**
PR (n=373)			
≤50	135 (44.3)	41 (60.3)	**0.017[x]**
>50	170 (55.7)	27 (39.7)	
HER2			
0	174 (56.5)	37 (52.1)	
1	65 (21.1)	15 (21.1)	0.715[x]
2	69 (22.4)	19 (26.8)	
Ki67	25 (1 - 90)	40 (5 - 100)	**<0.001[m]**
Ki67 (n=360)			
<20	94 (32.4)	7 (10)	**<0.001[x]**
≥20	196 (67.6)	63 (90)	
Surgery type (n=378)			
BCS+SLND	44 (14.3)[a]	23 (32.9)[b]	**<0.001[x]**
MRM+AD	166 (53.9)[a]	18 (25.7)[b]	
BCS+AD	68 (22.1)[a]	14 (20)[a]	
Mastectomy/MRM+SLND	30 (9.7)[a]	15 (21.4)[b]	
Adjuvant GnRH analogue (n=264)			
No	133 (60.5)	25 (56.8)	0.653[x]
Yes	87 (39.5)	19 (43.2)	
Adjuvant Hormonal Therapy (n=348)			
None	5 (1.8)[a]	5 (7.8)[b]	**0.038[f]**
TMX	134 (47.2)[a]	31 (48.4)[a]	
AI	145 (51.1)[a]	28 (43.8)[a]	

[m] Mann–Whitney U test (median [min–max]); [x] Pearson chi-square test; [f] Fisher's exact test. Values are presented as median (min–max) or n (%). Percentages represent within-group distributions. [a—b] Groups sharing the same superscript letter are not significantly different (Bonferroni-adjusted post hoc Z test).

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Abbreviations: pCR, pathological complete response; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; Ki-67, proliferation index; cT, clinical tumor stage; cN, clinical nodal stage; LVI, lymphovascular invasion; PNI, perineural invasion; BCS, breast-conserving surgery; SLND, sentinel lymph node dissection; AD, axillary dissection; MRM, modified radical mastectomy; TMX, tamoxifen; AI, aromatase inhibitor; GnRH, gonadotropin-releasing hormone.

Note: *Percentages were calculated using the number of evaluable patients for each variable. The corresponding denominators are indicated within the table where missing data were present.*

Firth Penalized Logistic Regression Analysis

Table 3 summarizes the results of the Firth penalized logistic regression analysis. In univariate analysis, ER expression >10% (compared to ≤10%), and increasing PR levels were associated with lower odds of achieving pCR. Conversely, Ki-67 ≥20% significantly increased the likelihood of pCR (OR=4.072, p<0.001).

In the multivariate model, which was statistically significant (Chi-square = 21.849, p=0.016), compared with ER ≤10%, both ER 10–40% (OR=0.06, p=0.011) and ER >40% (OR=0.125, p=0.014) were independently associated with reduced pCR probability. Ki-67 ≥20% remained independently associated with increased odds of achieving pCR (OR=2.999, p=0.031). PR level was not independently associated with pCR in the multivariate model.

Table 3. Univariate and Multivariate Firth Penalized Logistic Regression Analyses for Pathological Complete Response (pCR)

	Univariate		Multivariate	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
ER (Ref.: ≤10)				
10-40	0.22 (0.069 - 0.632)	**0.005**	0.06 (0.004 - 0.528)	**0.011**
>40	0.191 (0.089 - 0.41)	**<0.001**	0.125 (0.024 - 0.636)	**0.014**
PR	0.989 (0.981 - 0.996)	**0.001**	0.994 (0.982 - 1.006)	0.321
Ki-67 (Ref.: <20)	4.072 (1.948 - 9.77)	**<0.001**	2.999 (1.099 - 10.147)	**0.031**

OR: Odds ratio; CI: Confidence interval; Model statistics (multivariate model): Chi-square = 21.849, p = 0.016; Ref: Reference category; ER: Estrogen receptor; PR: Progesterone receptor; Ki-67: Proliferation index; pCR: Pathological complete response.

Event-Free Survival Analysis

During a median follow-up of 46.5 months (95% CI, 39.7–50.1) (estimated using the reverse Kaplan–Meier method), 69 events and 30 deaths occurred.

Kaplan–Meier survival analysis demonstrated significantly improved EFS in patients achieving pCR compared with those without pCR (log-rank p=0.002) (Figure 1A). EFS also differed significantly across regression score groups (p<0.001) (Figure 1B). Other significant variables were evaluated within Cox regression models.

As shown in Table 4, univariate Cox regression analysis for EFS demonstrated that older age was associated with improved EFS (HR=0.965, p=0.002), whereas advanced clinical stage (HR=1.747, p=0.030), the presence of LVI (HR=2.382, p=0.002), PNI (HR=1.890, p=0.027), and Ki-67 ≥20% (HR=2.516, p=0.011) were significantly associated with worse EFS. Higher

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pT and pN stages, particularly pT3 and pN3, were also associated with worse EFS. Adjuvant LHRH therapy was associated with worse EFS in univariate analysis (HR=2.403, p=0.003). In contrast, achieving pCR was significantly associated with improved EFS (HR=0.191, p=0.005).

Given that 69 recurrences occurred in the study population, and considering the rule-of-thumb of approximately 10 events per variable in Cox regression modeling, the number of candidate variables included in the multivariate analyses was limited to reduce the risk of overfitting. Furthermore, to minimize potential multicollinearity between highly correlated variables, two separate multivariate Cox regression models were constructed. In particular, pathological T and N stages were not included in the same multivariate model as clinical stage to avoid collinearity between pre-treatment and post-treatment variables.

In Multivariate Model 1, age (HR=0.965, p=0.005), Ki-67 ≥20% (HR=3.299, p=0.003), and pCR (HR=0.166, p=0.003) remained independently associated with EFS, while clinical stage retained borderline significance (HR=1.740, p=0.047).

In Multivariate Model 2, age (HR=0.963, p=0.009), LVI (HR=2.136, p=0.016), and pCR (HR=0.129, p=0.044) were independently associated with EFS. The effect of Ki-67 attenuated and lost statistical significance (p=0.057), and PNI was no longer independently associated with EFS (p=0.994).

Importantly, pCR consistently demonstrated the strongest independent association with improved EFS across both multivariate models.

The association observed with adjuvant LHRH therapy in univariate analysis likely reflects treatment allocation in higher-risk patients rather than a direct detrimental effect on EFS.

Table 4. Univariate and Multivariate Cox Proportional Hazards Regression Analyses for Event-Free Survival (EFS)

	Univariate		Multivariate Model 1		Multivariate Model 2	
	HR (%95 CI)	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age	0.965 (0.943 - 0.987)	**0.002**	0.965 (0.942 - 0.989)	**0.005**	0.963 (0.935 - 0.99)	**0.009**
Clinical stage (Ref.: Stage 2)	1.747 (1.057 - 2.889)	**0.030**	1.74 (1.007 - 3.007)	**0.047**		
LVI (Ref.: Absent)	2.382 (1.371 - 4.138)	**0.002**			2.136 (1.152 - 3.958)	**0.016**
PNI (Ref.: Absent)	1.89 (1.077 - 3.318)	**0.027**			0.997 (0.479 - 2.076)	0.994
ER	0.993 (0.987 - 1)	0.057				
PR	0.999 (0.993 - 1.005)	0.740				
Ki-67 (Ref.: <20)	2.516 (1.236 - 5.122)	**0.011**	3.299 (1.483 - 7.339)	**0.003**	2.241 (0.978 - 5.135)	0.057
pCR (Ref.: No)	0.191 (0.06 - 0.608)	**0.005**	0.166 (0.052 - 0.535)	**0.003**	0.129 (0.018 - 0.946)	**0.044**
pT (Ref.: 0)						
1	6.891 (1.657 - 28.659)	**0.008**				
2	5.431 (1.259 - 23.418)	**0.023**				
3	17.228 (3.717 - 79.839)	**<0.001**				
4	14.915 (2.489 - 89.375)	**0.003**				
pN (Ref.: 0)						

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1	1.572 (0.838 - 2.946)	0.159
2	1.415 (0.697 - 2.871)	0.337
3	6.929 (3.38 - 14.207)	**<0.001**
Adjuvant LHRH analogue (Ref.: None)	2.403 (1.338 - 4.318)	**0.003**
Adjuvant Hormonal Therapy (Ref.: None)		
TMX	0.682 (0.239 - 1.944)	0.474
AI	0.317 (0.107 - 0.938)	**0.038**

HR: Hazard ratio; CI: Confidence interval; Ref.: Reference category; EFS: Event-free survival; LVI: Lymphovascular invasion; PNI: Perineural invasion; ER: Estrogen receptor; PR: Progesterone receptor; pCR: Pathological complete response; LHRH: Luteinizing hormone–releasing hormone; TMX: Tamoxifen; AI: Aromatase inhibitor.

Model 1: Chi-square = 33.490, p < 0.001
Model 2: Chi-square = 27.027, p < 0.001

Figure 1. Kaplan–Meier curves for event-free survival (EFS). (A) Survival according to pathological complete response (pCR) status. (B) Survival according to regression score categories.

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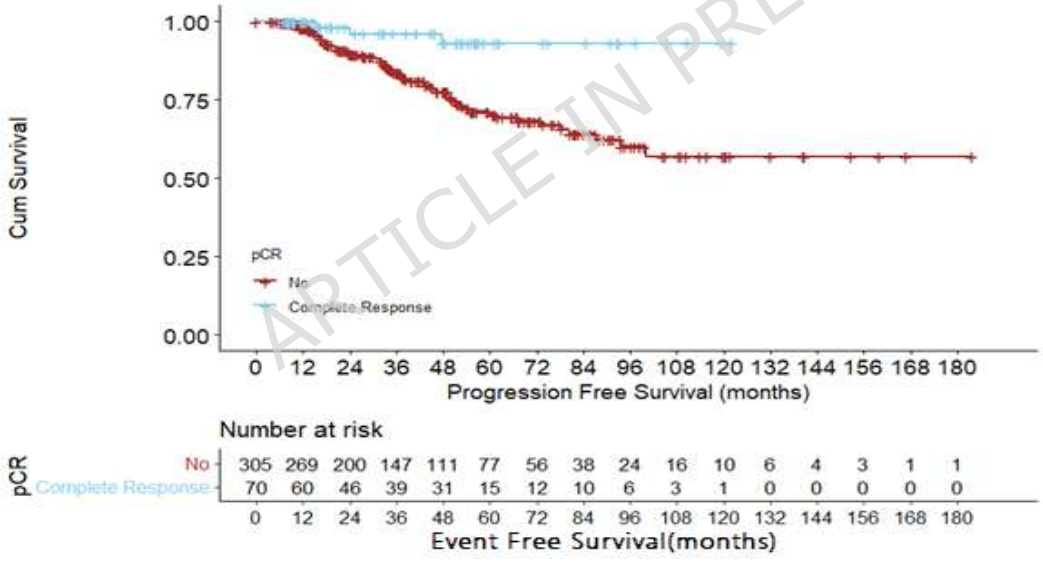


Figure 1A. Kaplan–Meier curves for event-free survival (EFS) according to pathological complete response (pCR) status, with numbers at risk. A significant difference in EFS was observed between groups (log-rank p=0.002). Patients who achieved pCR had significantly improved EFS compared with those without pCR. Median EFS was

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not reached in either group during the follow-up period.

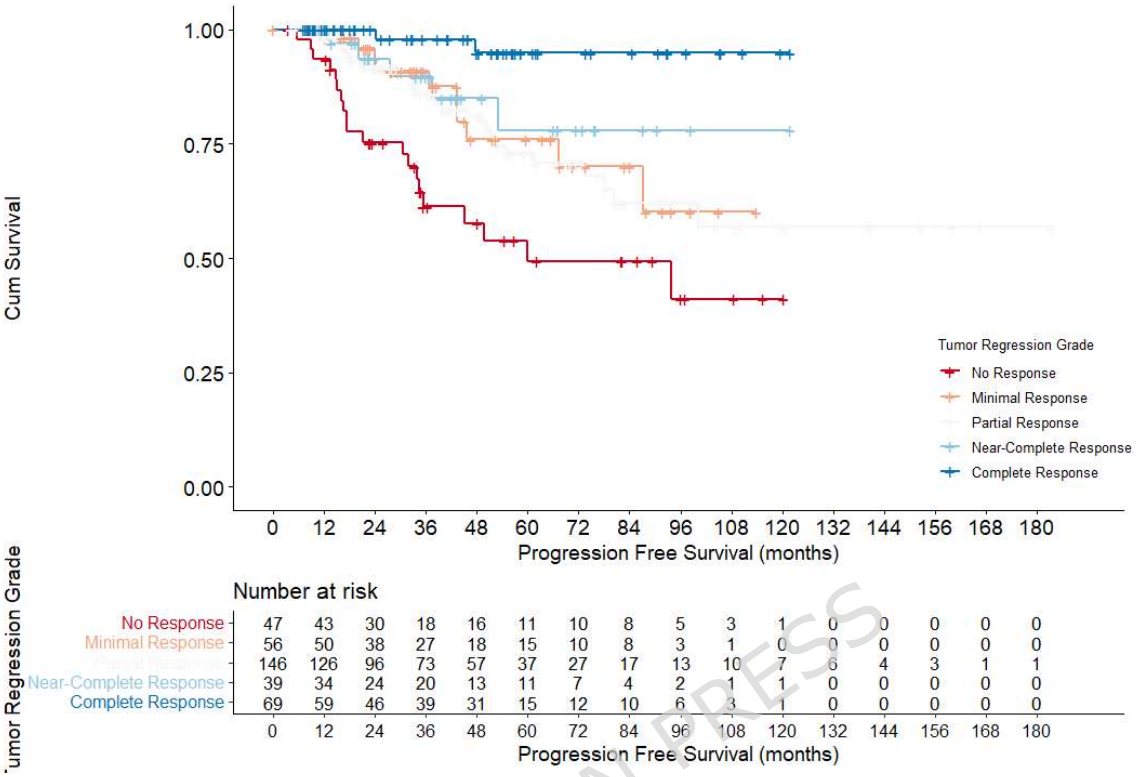


Figure 1B. Kaplan–Meier curves for event-free survival (EFS) according to regression score categories, with numbers at risk. EFS differed significantly across response groups (log-rank p<0.001). Median EFS was reached only in patients with no response (59.83 months, 95% CI: 9.11–110.55), while it was not reached in the other regression score categories during follow-up.

Overall Survival Analysis

Kaplan–Meier analysis demonstrated significantly improved OS in patients who achieved pCR compared with those without pCR (log-rank p=0.048) (Figure 2A). OS also differed significantly across regression score categories (log-rank p=0.002) (Figure 2B). Median OS was not reached in either group during follow-up. Other significant variables were evaluated within Cox regression models.

In univariate Cox regression analysis for OS, the presence of LVI was significantly associated with worse OS (HR=2.624, p=0.025). Higher ER expression was associated with improved OS (HR=0.988, p=0.022). Ki-67 ≥20% showed borderline significance (HR=4.302, p=0.050). Advanced nodal involvement (pN3) was strongly associated with worse OS (HR=5.787, p=0.002). Age, PR level, pCR, and pT stage were not significantly associated with OS in univariate analysis. pN1 and pN2 stages were also not significantly associated with OS.

Given that only 30 mortality events occurred in the cohort, the number of candidate variables included in the multivariate models was limited to reduce the risk of overfitting. To further minimize potential multicollinearity, two separate multivariate Cox regression models were constructed. The relatively small number of events in certain subgroups resulted in wide confidence intervals, which should be considered when interpreting the findings.

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In Multivariate Model 1 (Chi-square=25.005, p<0.001), higher ER expression remained independently associated with improved OS (HR=0.982, p=0.003), and pN3 disease remained significantly associated with worse OS (HR=4.618, p=0.015). LVI lost statistical significance in this model (p=0.078).

In Multivariate Model 2 (Chi-square=28.657, p<0.001), ER expression continued to be independently associated with improved OS (HR=0.976, p=0.001). LVI regained statistical significance (HR=3.285, p=0.041). Importantly, pN3 remained a strong independent factor associated with worse OS (HR=5.484, p=0.043).

Overall, ER expression was consistently associated with improved OS, while advanced nodal disease (pN3) emerged as the most robust determinant of worse OS across multivariate models.

Table 5. Univariate and Multivariate Cox Regression Analyses for Overall Survival (OS)

	Univariate		**Multivariate Model 1**		**Multivariate Model 2**	
	HR (%95 CI)	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age	0.992 (0.961 - 1.024)	0.624				
LVI (Ref.: Absent)	2.624 (1.13 - 6.09)	**0.025**	2.213 (0.914 - 5.362)	0.078	3.285 (1.048 - 10.298)	**0.041**
ER	0.988 (0.978 - 0.998)	**0.022**	0.982 (0.97 - 0.994)	**0.003**	0.976 (0.962 - 0.99)	**0.001**
PR	0.999 (0.989 - 1.008)	0.798				
Ki67 (Ref.: <20)	4.302 (1.001 - 18.495)	0.050			5.847 (0.727 - 47.038)	0.097
pCR (Ref.: No)	0.17 (0.023 - 1.254)	0.082				
pT (Ref.: 0)						
1	-	0.906				
2	-	0.906				
3	-	0.896				
4	-	0.897				
pN (Ref.: 0)						
1	1.6 (0.592 - 4.33)	0.354	0.949 (0.292 - 3.083)	0.931	1.706 (0.433 - 6.725)	0.446
2	1.599 (0.56 - 4.568)	0.381	1.293 (0.441 - 3.791)	0.640	0.875 (0.203 - 3.762)	0.857
3	5.787 (1.901 - 17.621)	**0.002**	4.618 (1.347 - 15.834)	**0.015**	5.484 (1.051 - 28.598)	**0.043**

HR: Hazard ratio; CI: Confidence interval; Ref.: Reference category; OS: Overall survival; LVI: Lymphovascular invasion; ER: Estrogen receptor; PR: Progesterone receptor; Ki-67: Proliferation index; pCR: Pathological complete response.
Model 1: Chi-square = 25.005, p < 0.001.
Model 2: Chi-square = 28.657, p < 0.001.

Figure 2. Kaplan–Meier curves for overall survival (OS). (A) Survival according to pathological complete response (pCR) status. (B) Survival according to regression score categories.

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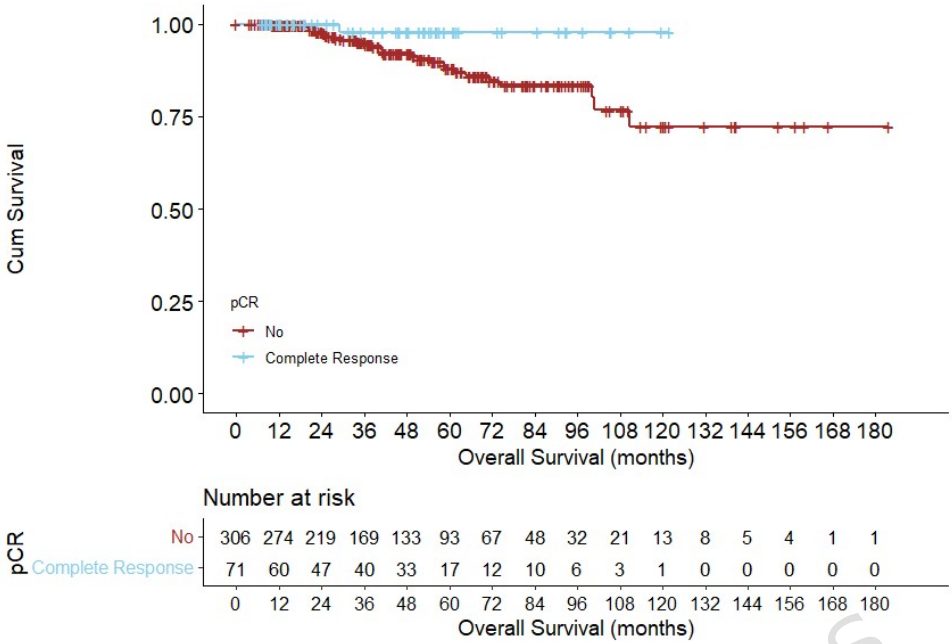


Figure 2A. Kaplan–Meier curves for overall survival (OS) according to pathological complete response (pCR) status, with numbers at risk. A significant difference in OS was observed between the groups (log-rank p=0.048). Patients who achieved pCR demonstrated improved OS compared with those without pCR.

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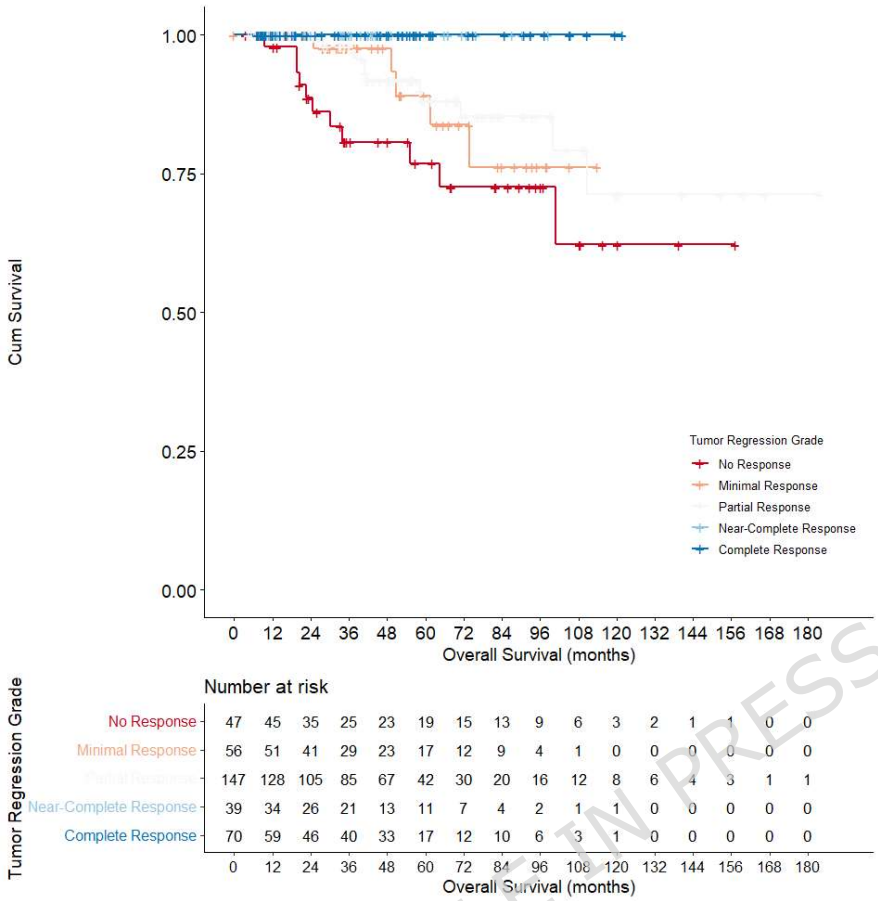


Figure 2B. Kaplan–Meier curves for overall survival (OS) according to regression score categories, with numbers at risk. OS differed significantly across response groups (log-rank p=0.002).

Discussion

In this multicenter study, we evaluated predictors of pCR and its prognostic implications in patients with HR-positive/HER2-negative breast cancer treated with NAC. Our study provides additional real-world evidence by simultaneously evaluating predictors of pCR and its independent prognostic significance for both EFS and OS in a multicenter cohort. Our findings highlight three key observations. First, pCR rates remained low in HR-positive/HER2-negative disease. Second, quantitative ER expression and proliferative activity were key determinants of chemotherapy responsiveness. Third, although achieving pCR was independently associated with improved EFS, it did not independently predict OS. These findings provide further evidence that the prognostic significance of pCR in HR-positive/HER2-negative breast cancer differs according to the clinical outcome assessed, supporting its role as a surrogate marker for recurrence-related outcomes rather than long-term survival.

Lower ER expression was strongly associated with higher pCR rates in our cohort. However, this enhanced chemosensitivity did not translate into a proportional improvement in EFS, underscoring the biological distinction between chemotherapy responsiveness and long-term endocrine-driven disease control in HR-positive/HER2-negative breast cancer. Tumors with ER ≤10% likely represent a more proliferative and less endocrine-dependent phenotype, which may

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explain their increased sensitivity to cytotoxic therapy. Nevertheless, reduced endocrine dependency may also limit sustained disease control after completion of systemic treatment. Conversely, tumors with high ER expression demonstrated lower pCR rates yet more favorable survival outcomes, highlighting the dominant prognostic role of intrinsic endocrine sensitivity in this subgroup. These findings are consistent with prior evidence suggesting that quantitative ER expression reflects underlying tumor biology and may refine risk stratification beyond binary hormone receptor classification [8,14,19].

Our findings also suggest that quantitative ER assessment may have practical implications for neoadjuvant treatment selection. Patients with strongly ER-positive tumors are biologically more endocrine-responsive and may derive less benefit from chemotherapy. Previous studies have shown that neoadjuvant endocrine therapy, particularly with aromatase inhibitors, can effectively reduce tumor volume and increase BCS rates in postmenopausal women with ER-rich breast cancer [11–13]. Therefore, quantitative ER expression, together with proliferative markers such as Ki-67, may help guide the selection of neoadjuvant endocrine therapy versus chemotherapy, thereby supporting a more individualized treatment approach.

Although lower PR expression was associated with higher pCR rates in univariate analyses, it did not retain independent predictive significance in multivariable modeling. This observation is consistent with prior evidence indicating that PR loss may reflect underlying tumor aggressiveness and reduced endocrine sensitivity rather than functioning as an independent determinant of chemotherapy response [8,19-22]. Several studies have suggested that the prognostic and predictive impact of PR expression diminishes once proliferative activity and intrinsic subtype are taken into account.

Consistent with this interpretation, Ki-67 emerged as one of the strongest independent correlates of pCR. Tumors with Ki-67 ≥20% demonstrated significantly greater likelihood of achieving pCR, reinforcing the concept that proliferation is central to chemotherapy responsiveness in HR-positive disease [23-24]. These findings align with molecular subtype data indicating that luminal B tumors—characterized by higher proliferative indices—exhibit greater chemosensitivity compared with luminal A tumors [25-27]. Our results therefore support the view that HR-positive/HER2-negative breast cancer should not be managed as a homogeneous entity in the neoadjuvant setting but rather stratified according to biological risk features.

Regarding survival outcomes, achieving pCR was significantly associated with improved EFS but did not independently predict OS. While pCR consistently emerged as the strongest independent predictor of EFS in multivariable analyses, this effect did not translate into an independent OS benefit after adjustment for established pathological risk factors. Although Kaplan–Meier analysis demonstrated a significant OS difference according to pCR status, this association did not persist in adjusted models, suggesting that the apparent survival advantage may be largely driven by residual nodal burden and intrinsic tumor biology rather than reflecting a direct independent effect of pCR itself.

This divergence between recurrence-related outcomes and overall survival has been consistently reported in HR-positive breast cancer [2,4,28]. Unlike triple-negative or HER2-

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positive disease, HR-positive tumors are characterized by a prolonged natural history, ongoing risk of late recurrence, and sustained benefit from adjuvant endocrine therapy [6,7,29]. Consequently, the prognostic impact of pCR on overall survival may be attenuated by long-term endocrine responsiveness and the availability of effective subsequent therapies. In addition, the median follow-up duration was 46.5 months, which may be insufficient to fully capture late survival events. Furthermore, only 30 deaths occurred during follow-up and the median OS was not reached, limiting the statistical power to detect a modest independent association between pCR and OS.

In our cohort, older age and achieving pCR were independently associated with improved EFS, whereas higher proliferative index (Ki-67 ≥20%) and the presence of LVI were associated with worse outcomes in multivariable analyses. Advanced clinical stage was also associated with worse EFS in univariate analysis and retained borderline significance after adjustment. The inverse association between age and EFS events may reflect the more aggressive tumor biology frequently observed in younger patients with luminal breast cancer. Collectively, these findings suggest that early recurrence risk in HR-positive/HER2-negative disease is shaped by the interplay between intrinsic tumor biology, baseline disease burden, and treatment response, as reflected by pCR status [14,27,28]. Furthermore, prior studies have demonstrated that the interaction between age, proliferative activity, and tumor biology influences recurrence dynamics in hormone receptor–positive breast cancer [8,30].

In contrast, overall survival in our analysis was more strongly influenced by classical pathological factors. Advanced nodal involvement, particularly pN3 disease, emerged as the most robust independent determinant of mortality, underscoring the central prognostic importance of residual nodal burden after NAC [14,27,28]. ER expression demonstrated a consistent protective association with OS, consistent with the well-established favorable prognosis of endocrine-responsive tumors and their sustained benefit from adjuvant endocrine therapy [6,7]. LVI also independently predicted worse OS in multivariable analysis, reinforcing its role as a marker of systemic dissemination and aggressive tumor biology [31-33]. Given the relatively small number of mortality events, multivariate models were constructed cautiously to minimize overfitting, and findings should be interpreted within this context.

Taken together, these findings highlight the biological heterogeneity of HR-positive/HER2-negative breast cancer in the neoadjuvant setting. While pCR reflects chemosensitivity and confers improved EFS, long-term survival appears to be predominantly governed by intrinsic endocrine sensitivity and the extent of residual nodal disease. These findings further support the concept that pCR should not be interpreted as a universal surrogate for long-term survival in HR-positive/HER2-negative breast cancer, but rather as a marker of early treatment response within a biologically diverse disease [34].

Limitations

Several limitations of this study should be acknowledged. First, the retrospective design inherently introduces the potential for selection bias and unmeasured confounding, despite the inclusion of consecutive eligible patients from three tertiary centers. Although the multicenter nature of the study enhances generalizability, differences in institutional practices, patient

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referral patterns, and treatment approaches over the extended study period (2010–2025) may have contributed to heterogeneity.

Second, the relatively small number of mortality events may have reduced the statistical power of the overall survival analyses and increased the risk of overfitting in multivariable models. To mitigate this risk, the number of variables included in each model was restricted according to the number of outcome events, and separate models were constructed to minimize potential multicollinearity. Nevertheless, these findings should be interpreted with caution, and the possibility of a Type II error, particularly in the multivariable analyses of overall survival, cannot be excluded.

Additionally, missing data for certain pathological variables may have introduced potential bias, although analyses were performed using available-case methodology.

Additionally, ER and PR expression were categorized using predefined thresholds for exploratory analyses. Although the ≤10% ER threshold was based on the established ER-low category, the >40% ER and 50% PR cutoffs were selected to facilitate subgroup stratification and provide balanced subgroup sizes. Accordingly, these thresholds should be considered exploratory, may be dataset-specific, and require validation in independent cohorts.

Finally, adjuvant endocrine therapy and ovarian suppression were administered according to clinical judgment and prevailing guidelines, introducing the possibility of treatment allocation bias. In particular, ovarian suppression with LHRH analogs was preferentially administered to selected premenopausal patients with higher-risk disease characteristics, which may have confounded its apparent association with poorer EFS. Consequently, associations observed between adjuvant therapies and survival outcomes should be interpreted within this context.

External validation of our findings was not available; therefore, the generalizability of the observed associations requires further confirmation. Future prospective multicenter studies incorporating independent validation cohorts and contemporary molecular profiling are warranted to determine whether quantitative ER expression and proliferative activity can be reliably integrated into treatment selection algorithms. Before these biomarkers can be incorporated into routine clinical practice, their predictive performance and clinical utility should be prospectively validated using standardized biomarker assessment and predefined treatment algorithms in independent patient populations.

Despite these limitations, the relatively large sample size, extended follow-up duration, and use of robust statistical modeling approaches strengthen the validity of our findings.

Declarations

Author Contributions: Concept and design: Esma Uguztemur, Data collection: Esma Uguztemur, Esra Asik, Ozgur Arici, Ece Karanci, Atila Yildirim, Data analysis and interpretation: Esma Uguztemur, Manuscript drafting: Esma Uguztemur, Critical revision of the manuscript: All authors, Final approval of the manuscript: All authors.

Conflict of Interest: The author declares no conflict of interest.

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Informed Consent: Due to the retrospective design of the study, informed consent was waived by the ethics committee.

Data Availability Statement: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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