The Breast 81 (2025) 104449

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

Comparison of oncological outcomes of premenopausal with ovarian function suppression versus postmenopausal women in ER+/HER2- breast cancer

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ARTICLE INFO

Keywords:
Estrogen receptor–positive
Breast cancer
Premenopausal
Postmenopausal
Ovarian function suppression
Invasive disease–free survival
Distant relapse–free survival

ABSTRACT

Background: The Rx for positive node endocrine-responsive breast cancer trial highlighted that premenopausal (PRE) women who underwent chemotherapy exhibited superior survival rates compared to postmenopausal (POST) counterparts, but showed worse survival without chemotherapy. This raises the question whether application of ovarian function suppression (OFS) in PRE women aligns with their cancer biology, treatment response, and outcomes observed in POST women.

Methods: Data from the Seoul National University Hospital breast cancer cohort focusing on patients with stage pT1-3, pN0-1, estrogen receptor-positive (ER+), and HER2-negative breast cancer were analyzed. Survival outcomes, including invasive disease-free survival (iDFS) and distant relapse-free survival (DRFS), were compared between PRE women receiving OFS and POST women, with chemotherapy usage as a stratification factor. Propensity score matching was performed.

Result: We analyzed 3483 patients, comprising 2901 POST and 582 PRE women with OFS. In the cohort without chemotherapy, the 10-year iDFS rates were 90.3 % and 88.3 % (hazard ratio [HR], 1.32; $p = 0.16$), and 10-year DRFS rates were 94.3 % and 96.1 % (HR, 0.78; $p = 0.41$) for POST and PRE women with OFS, respectively. Among women treated with chemotherapy, 10-year iDFS rates were 83.0 % and 79.5 % (HR, 1.21; $p = 0.37$), and DRFS rates were 86.7 % and 85.7 % (HR, 1.14; $p = 0.58$) for POST and PRE women with OFS, respectively. These results remained consistent after PSM.

Conclusion: Oncological outcomes of PRE women receiving OFS were comparable to those of POST women with ER+ and HER2-early breast cancer, irrespective of chemotherapy administration.

1. Introduction

Precise estimation of prognosis has led to more tailored adjuvant treatment for women with estrogen receptor-positive (ER+) and human epidermal growth factor receptor 2 (HER2)-negative breast cancer. The trial assigning individualized options for treatment (TAILORx) demonstrated that in women aged >50 years with a midrange 21-gene recurrence score, adjuvant endocrine therapy alone was noninferior to chemoendocrine therapy for invasive disease-free survival (iDFS). However, younger women with recurrence scores between 16 and 25 benefited from the addition of chemotherapy, emphasizing the role of age and hormonal status in treatment decisions [1,2]. Similarly, the Rx for positive node endocrine-responsive breast cancer (RxPONDER) trial extended these findings to patients with positive lymph nodes, showing that premenopausal (PRE) women experienced improved iDFS and distant relapse-free survival (DRFS) with chemoendocrine therapy, whereas postmenopausal (POST) women did not [3,4].

These landmark trials confirmed the clinical utility of multigene

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https://doi.org/10.1016/j.breast.2025.104449
Received 5 February 2025; Received in revised form 15 March 2025; Accepted 16 March 2025
Available online 17 March 2025

prognostic assays and successfully identified women who could benefit from adjuvant chemotherapy; however, they also raised the question of whether differences in chemotherapy benefit among PRE and POST are due to the direct cytotoxic effects of chemotherapy or chemotherapy-induced menopause, which may act similarly to ovarian function suppression (OFS).

Meanwhile, it is well-established that PRE women often face more aggressive disease, higher recurrence rates, and lower survival, with chemotherapy-induced amenorrhea providing a significant survival benefit [5–10]. More recent studies, including the SOFT/TEXT trials, have demonstrated that combining OFS with tamoxifen or aromatase inhibitors improves outcomes in PRE women [11–15]. However, it remains unclear whether PRE women with OFS achieve prognoses and treatment responses similar to those of POST counterparts.

Our study aimed to determine whether PRE women treated with OFS, regardless of the administration of chemotherapy, had outcomes comparable to those of POST women with ER-positive, and HER2-negative breast cancer.

2. Materials and methods

2.1. Study design

This retrospective study reviewed the clinicopathological and treatment records of patients who underwent breast cancer surgery between January 2000 and December 2018 at Seoul National University Hospital (SNUH). Eligible patients were those with ER-positive, HER2-negative breast cancer who underwent primary surgery, had pathological T1-2 and N0-1 staging, and received adjuvant endocrine treatment. Male patients with breast cancer, those who did not undergo axillary surgery, and those who did not receive standard adjuvant endocrine therapy were excluded. The Institutional Review Board of SNUH approved this study. The requirement for informed consent was waived because of the retrospective nature of the study, which posed no potential harm to the included patients.

2.2. Patient characteristics

The baseline clinicopathological data were extracted from our institution's comprehensive database and electronic medical records. Tumor-node-metastasis staging was performed according to the eighth edition of the American Joint Committee on Cancer criteria [16]. ER status was assessed by immunohistochemistry and was considered positive if more than 1 % of the cells stained positive. HER2 status was assessed using anti-HER2 antibodies and confirmed by fluorescence in situ hybridization or silver-enhanced in situ hybridization if equivocal. Ki-67 expression was classified as high if more than 10 % of tumor cells were stained [17].

The patients were categorized into two cohorts: those receiving adjuvant endocrine therapy alone and those receiving adjuvant chemoendocrine therapy. Menopause was determined before the chemotherapy or any hormonal therapy with the general definition as follows: 1) before bilateral oophorectomy, 2) age $\geq$60 years, and 3) age <60 with amenorrhea for $\geq$12 months and estradiol and follicle-stimulating hormone (FSH) in the POST range. In this study, we included only those younger than 50 years of age who underwent OFS for at least 6 months in the PRE with OFS group.

2.3. Statistical analysis

Continuous variables were analyzed using the Mann-Whitney *U* test, while categorical variables were analyzed using Pearson's χ^2 test. Survival rates were calculated using the Kaplan–Meier method, and comparisons between groups were made using the log-rank test. Statistical significance was defined as a p-value of <0.05. All analyses were performed using the R software version 4.0.0 (The R Foundation for Statistical Computing, Vienna, Austria).

To account for a potential selection bias, propensity score matching (PSM) was performed. The nearest-neighbor matching method was used for 1:1 matching without replacement, applying a caliper width of 0.10 standard deviations of the logit of the propensity scores. Matching variables included the year of surgery (operation year), tumor (T) stage, and nodal (N) stage to ensure comparability between the groups based on key prognostic factors. Survival outcomes were further analyzed using the Cox proportional hazards model to estimate hazard ratios (HRs) with 95 % confidence intervals (CIs). The primary outcome was iDFS. The iDFS events included local, regional, or distant recurrences of invasive breast cancer and secondary primary breast cancer, including death. The secondary outcome was DRFS, defined as the time from surgery to the first distant recurrence, excluding cases of death without distant recurrence.

3. Results

3.1. Patient characteristics

Overall, 3483 patients met the inclusion criteria (Fig. 1). The patients were grouped into endocrine-only therapy (N = 2210) and chemoendocrine therapy (N = 1273) cohorts. In the endocrine therapy cohort, 1793 POST women and 417 PRE women received OFS (PRE_OFS). The median age in the POST group was 57 years (IQR 53–62), compared to 44 years (IQR 39–47) for PRE_OFS (Table 1). Higher body mass index (BMI) was observed in the POST group (median 24.0, IQR 21.9–26.2) compared to the PRE_OFS group (median 21.7, IQR 20.1–23.8; p < 0.001). Total mastectomy with or without reconstruction was more common in the PRE_OFS group (26.1 %) than in the POST group (21.2 %). Pathologic N1 (vs. N0) stage was more common in the PRE_OFS than in the POST group (8.6 % vs. 4.7 %, p = 0.002).

In the chemoendocrine therapy cohort, 1110 were POST and 163 were PRE_OFS. The POST group had a higher median age (56 years, IQR 52.0–60.0) than the PRE_OFS group (35 years, IQR 30.5–38.0). BMI was similarly higher in the POST group (median 24, IQR 22.1–26.4, p <

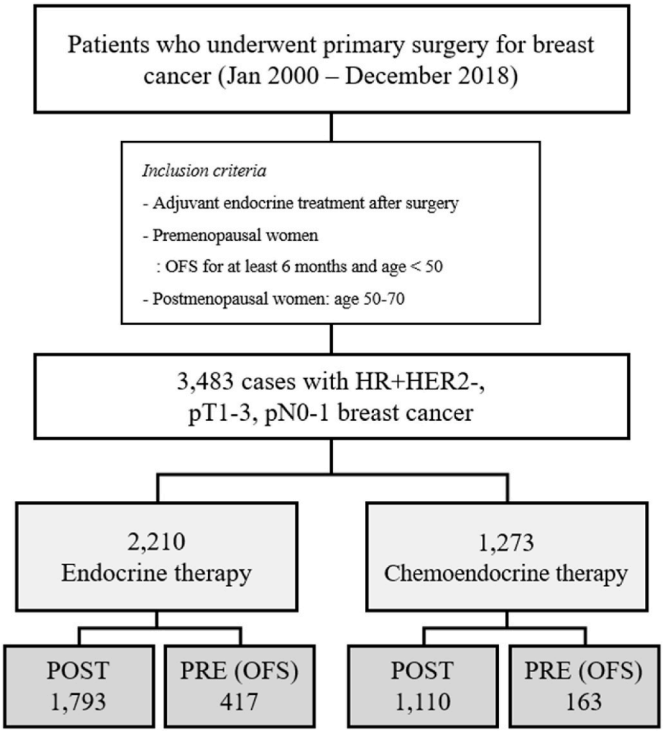


Fig. 1. Flow diagram of patients' enrollment.

Table 1
Clinicopathologic characteristics.

	Endocrine therapy alone				Chemoendocrine therapy			
	Before PSM		After PSM		Before PSM		After PSM	
	Postmenopause	Premenopause	Postmenopause	Premenopause	Postmenopause	Premenopause	Postmenopause	Premenopause
	(N = 1793)	(N = 417)	(N = 394)	(N = 394)	(N = 1110)	(N = 163)	(N = 151)	(N = 151)
Age, years (IQR)	57.0 (53.0, 62.0)	44.0 (39.0, 47.0)	58.0 (52.0, 63.0)	44.0 (39.0, 47.0)	56.0 (52.0, 60.0)	35.0 (30.5, 38.0)	55.0 (52.0, 59.0)	35.0 (30.0, 37.5)
BMI (IQR)	24.0 (21.9, 26.2)	21.7 (20.1, 23.8)	23.9 (22.1, 26.3)	21.7 (20.1, 23.8)	24.0 (22.1, 26.4)	20.9 (19.1, 23.5)	23.9 (22.1, 26.2)	20.9 (19.0, 23.4)
Breast surgery								
BCS	1413 (78.8 %)	308 (73.9 %)	322 (81.7 %)	292 (74.1 %)	727 (65.5 %)	102 (62.6 %)	117 (77.5 %)	92 (60.9 %)
TM	380 (21.2 %)	109 (262.1 %)	72 (18.3 %)	102 (25.9 %)	383 (34.5 %)	61 (37.4 %)	34 (22.5 %)	59 (39.1 %)
Axillary surgery								
SLNB	1556 (86.8 %)	369 (88.5 %)	355 (90.1 %)	348 (88.3 %)	563 (50.7 %)	112 (68.7 %)	103 (68.2 %)	100 (66.2 %)
ALND	237 (13.2 %)	48 (11.5 %)	39 (9.9 %)	46 (11.7 %)	547 (49.3 %)	51 (31.3 %)	48 (31.8 %)	51 (33.8 %)
Pathologic T								
T1	1524 (85.0 %)	347 (83.2 %)	327 (83.0 %)	327 (83.0 %)	528 (47.6 %)	88 (54.0 %)	80 (53.0 %)	80 (53.0 %)
T2	262 (14.6 %)	69 (16.5 %)	66 (16.8 %)	66 (16.8 %)	551 (49.6 %)	74 (45.4 %)	70 (46.4 %)	70 (46.4 %)
T3	7 (0.4 %)	1 (0.2 %)	1 (0.3 %)	1 (0.3 %)	31 (2.8 %)	1 (0.6 %)	1 (0.7 %)	1 (0.7 %)
Pathologic N								
N0	1709 (95.3 %)	381 (91.4 %)	358 (90.9 %)	358 (90.9 %)	548 (49.4 %)	98 (60.1 %)	87 (57.6 %)	87 (57.6 %)
N1	84 (4.7 %)	36 (8.6 %)	36 (9.1 %)	36 (9.1 %)	562 (50.6 %)	65 (39.9 %)	64 (42.4 %)	64 (42.4 %)
Ki-67								
Low	1681 (93.8 %)	398 (95.4 %)	362 (91.9 %)	375 (95.2 %)	928 (83.6 %)	130 (79.8 %)	122 (80.8 %)	120 (79.5 %)
High	103 (5.7 %)	19 (4.6 %)	32 (8.1 %)	19 (4.8 %)	168 (15.1 %)	31 (19.0 %)	29 (19.2 %)	31 (20.5 %)
Unknown	9 (0.5 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	14 (1.3 %)	2 (1.2 %)	0 (0.0 %)	0 (0.0 %)
Histologic Grade								
I	428 (23.9 %)	82 (19.6 %)	93 (23.6 %)	80 (20.3 %)	103 (9.3 %)	14 (8.6 %)	10 (6.6 %)	14 (9.3 %)
II	1123 (62.6 %)	277 (66.4 %)	255 (64.7 %)	275 (69.8 %)	593 (53.4 %)	81 (49.7 %)	91 (60.3 %)	80 (53.0 %)
III	168 (9.4 %)	40 (9.6 %)	46 (11.7 %)	39 (9.9 %)	350 (31.5 %)	57 (35.0 %)	50 (33.1 %)	57 (37.7 %)
Unknown	74 (4.1 %)	18 (4.3 %)	0 (0.0 %)	0 (0.0 %)	64 (5.8 %)	11 (6.7 %)	0 (0.0 %)	0 (0.0 %)

0.001). Pathologic N1 (vs. N0) stage was more common in the POST group (50.6 % vs. 39.9 %, p = 0.013).

After PSM, BMI and breast-conserving surgery rates were significantly higher in the POST groups than in the PRE_OFS group in both the endocrine therapy–alone and chemoendocrine therapy cohorts.

3.2. iDFS and DRFS

In the endocrine therapy cohort of 2210 patients, no significant difference was observed in iDFS (Hazard ratio (HR) 1.32, 95 % CI 0.90–1.94, p = 0.16) or DRFS (HR 0.78, 95 % CI 0.43–1.42, p = 0.41) between POST and PRE_OFS (Fig. 2a and b). These results remained consistent after PSM. No significant difference was observed in iDFS (HR 1.26, 95 % CI 0.75–2.13, p = 0.38) or DRFS (HR 0.74, 95 % CI 0.36–1.53, p = 0.42) between POST and PRE_OFS (Fig. 2c and d).

Similarly, in the chemoendocrine therapy cohort of 1273 patients, there were no significant differences in iDFS or DRFS between POST and PRE_OFS. HR for iDFS was 1.21 (95 % CI 0.80–1.83, p = 0.37) and for DRFS was 1.14 (95 % CI 0.71–1.86, p = 0.58) (Fig. 3a and b). After PSM, the survival differences were not significant, with HR for iDFS of 1.70 (95 % CI 0.91–3.16, p = 0.09) and for DRFS of 1.79 (95 % CI 0.85–3.76, p = 0.12) (Fig. 3c and d).

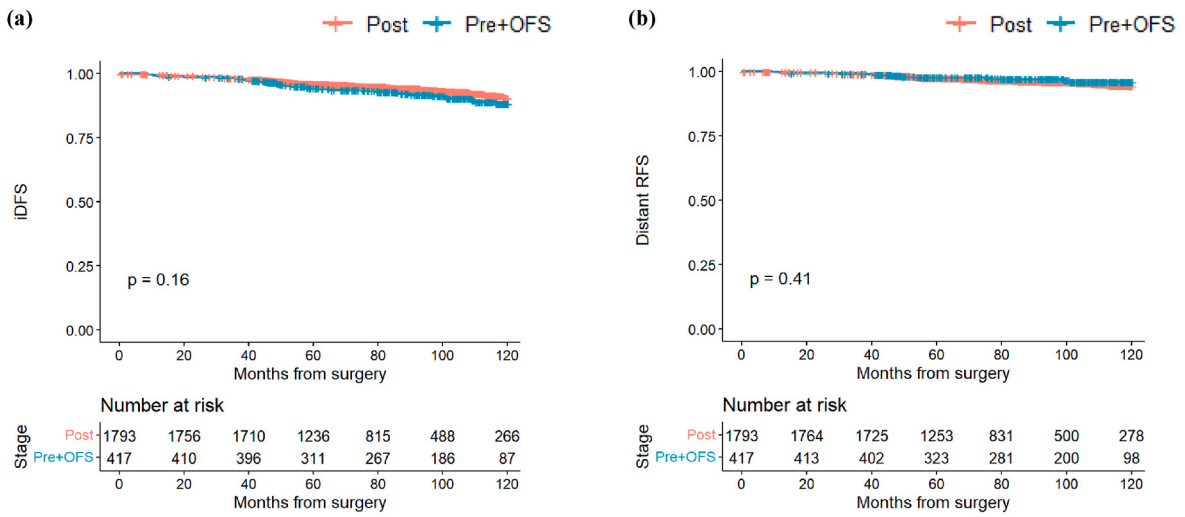
4. Discussion

The management of ER-positive and HER2-negative breast cancer in PRE women has been evolving, with ongoing debates surrounding the optimal use of chemotherapy and endocrine therapy. The RxPONDER trial demonstrated that PRE women had significantly better 5-year iDFS when chemotherapy was added to endocrine therapy (93.9 % vs. 89.0 % for endocrine therapy alone), whereas POST women did not show a comparable benefit from chemotherapy (91.3 % vs. 91.9 % for endocrine therapy alone) [3]. A remarkable finding of this study was that the 5-year iDFS and DRFS of POST women (91.9 % and 94.4 %, respectively) were better than those of PRE women (89.0 % and 92.8 %, respectively) with endocrine treatment alone. However, with the addition of chemotherapy, the 5-year iDFS and DRFS of POST women (91.3 % and 94.4 %, respectively) were worse than those of PRE women (93.9 % and 96.1 %, respectively). This raises the question of whether a biological distinction between cancer cells based on the host's menopausal status, such as differences in aggressiveness or endocrine/chemotherapy responses. Another important question is whether changing the hormonal milieu of PRE women through OFS to that of POST hosts could result in identical clinical outcomes.

Our study aimed to address this gap by evaluating whether OFS, when added to endocrine therapy, could equalize survival outcomes between PRE and POST women, independent of chemotherapy administration. The results from our cohort suggest that OFS may align with iDFS and DRFS outcomes in PRE and POST women.

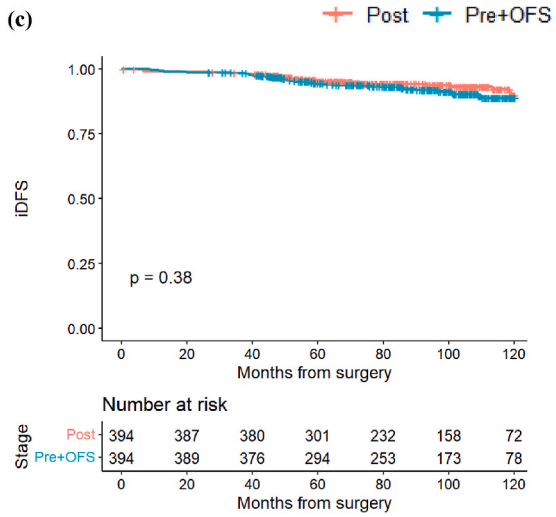
In the endocrine therapy cohort, we observed no significant differences in iDFS or DRFS between PRE_women receiving OFS and POST women before and after PSM. These results suggest that OFS alone may be sufficient to counteract the biological aggressiveness often associated with the PRE status, potentially reducing the need for chemotherapy in certain patients. This finding aligns with the results of the SOFT and TEXT trials, in which the combination of OFS with tamoxifen or an aromatase inhibitor significantly improved outcomes in PRE women compared with tamoxifen alone.

In the chemoendocrine therapy cohort, although not statistically significant, our study showed a worse trend in iDFS and DRFS in PRE women receiving OFS than in POST women. After PSM, the HRs for iDFS were 1.70 (p = 0.09) and for DRFS was 1.79 (p = 0.12), respectively. The first possible reason for the chemoendocrine group is selection bias. Since OFS was not randomly assigned, physicians may have been more likely to prescribe OFS to patients perceived to have a higher baseline risk, which may not have been fully adjusted for in the PSM process. Furthermore, patients who experienced chemotherapy-induced ovarian failure (CIOF) showed better DFS than those without CIOF (4-year DFS, 61.8 % vs. 87.5 %; HR, 2.69) [18]. In our study, it is likely that some patients who experienced CIOF—and therefore had a favorable

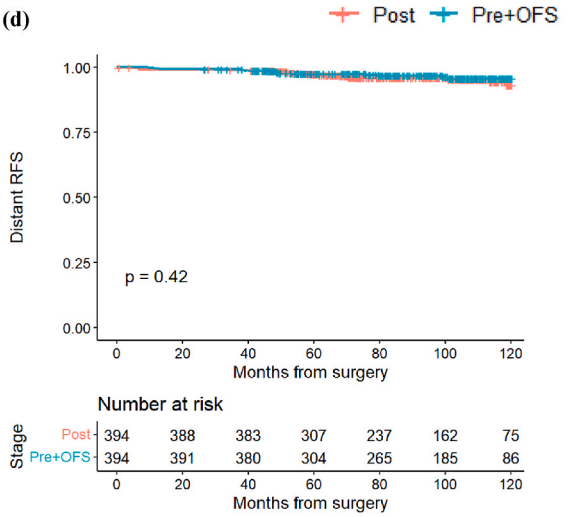


	Post	Pre (OFS)
# Events	100	35
HR (95% CI)	1.32 (0.90–1.94), p=0.16	
5-yr estimate	96.1%	94.3%
10-yr estimate	90.3%	88.3%

	Post	Pre (OFS)
# Events	62	13
HR (95% CI)	0.78 (0.43–1.42), p=0.41	
5-yr estimate	97.6%	97.7%
10-yr estimate	94.3%	96.1%



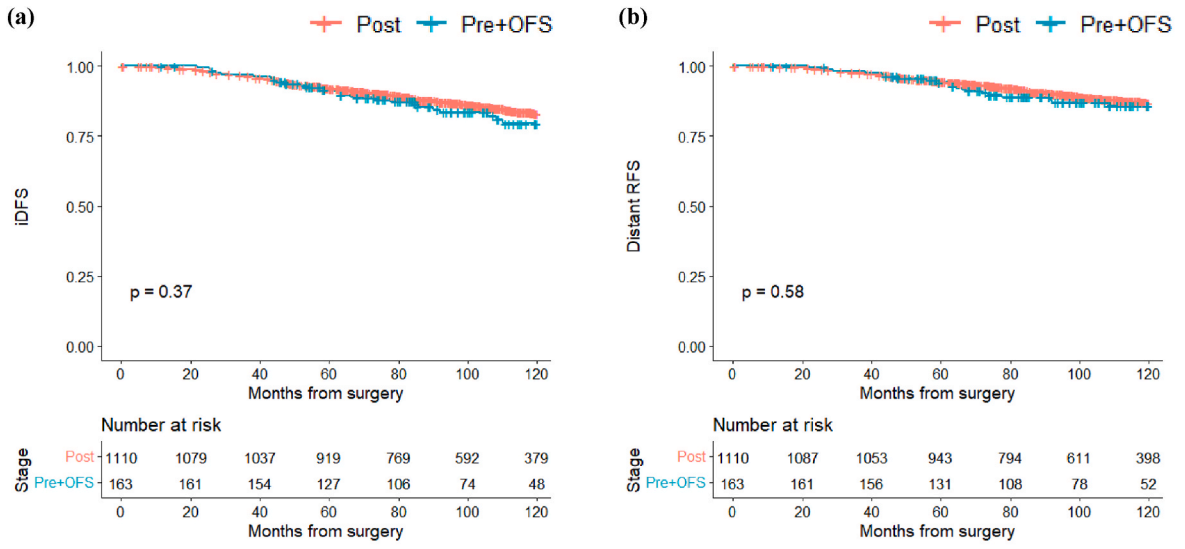
	Post	Pre (OFS)
# Events	25	32
HR (95% CI)	1.26 (0.75–2.13), p=0.38	
5-yr estimate	95.4%	94.5%
10-yr estimate	89.9%	88.9%



	Post	Pre (OFS)
# Events	17	13
HR (95% CI)	0.74 (0.36–1.53), p=0.42	
5-yr estimate	97.3%	97.6%
10-yr estimate	93.2%	95.8%

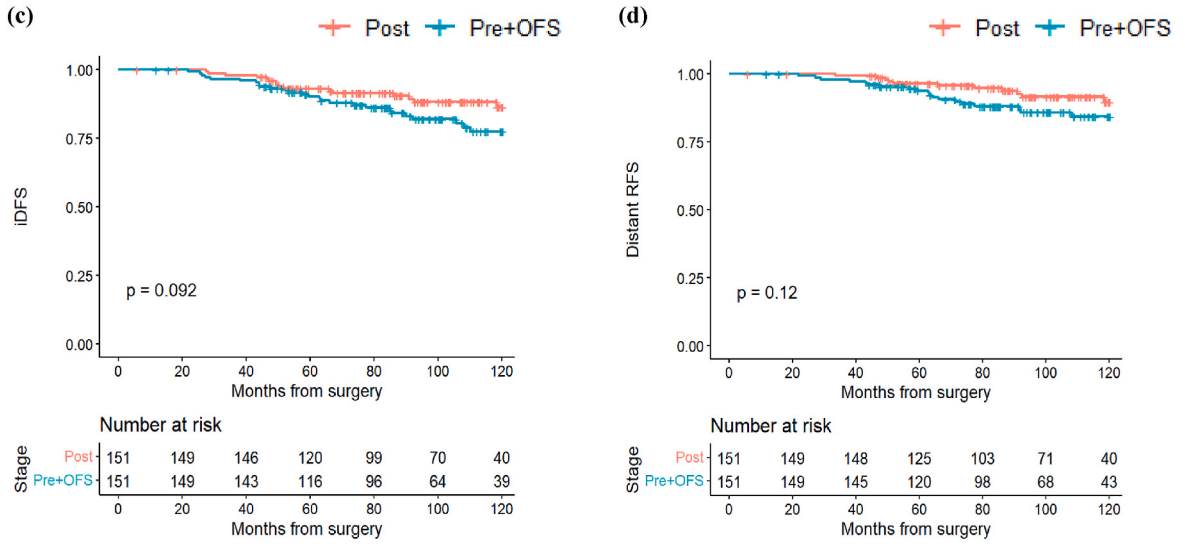
Fig. 2. Survival analysis of patients with adjuvant endocrine therapy only. (a) invasive Disease Free Survival (iDFS) of premenopausal patients with OFS and postmenopausal patients. (b) Distant recurrence free survival (DRFS) of patients with adjuvant endocrine therapy only. (c) After PSM, iDFS of patients with adjuvant endocrine therapy. (d) After PSM, DRFS of patients with adjuvant endocrine therapy.

prognosis—did not receive OFS and were consequently excluded from the OFS group. This selection pattern may have influenced the observed results in the chemoendocrine therapy subgroup, potentially contributing to the observed trends. The second reason was the very young age of the PRE chemoendocrine therapy group in our study (median age 35.0 years, Table 1). In an 8-year analysis of the SOFT trial [12], the OFS benefit was greatest in the age group <35. However, the 8-year DFS was worse in the age group <35 (second worst in the age 35–39) even with the addition of OFS. Breast cancer arising at an extremely young age is more aggressive and has potentially unique biological features [6,19]. These young patients may require more than simply inducing a POST hormonal state, necessitating specialized treatment. Azim et al. proposed therapeutic approaches such as targeting RANKL or mammary stem cells [20].



	Post	Pre (OFS)
# Events	154	26
HR (95% CI)	1.21 (0.80–1.83), p=0.37	
5-yr estimate	92.0%	91.0%
10-yr estimate	83.0%	79.5%

	Post	Pre (OFS)
# Events	119	19
HR (95% CI)	1.14 (0.71–1.86), p=0.58	
5-yr estimate	94.3%	94.2%
10-yr estimate	86.7%	85.7%



	Post	Pre (OFS)
# Events	16	26
HR (95% CI)	1.70 (0.91–3.16), p=0.09	
5-yr estimate	93.1%	90.3%
10-yr estimate	86.4%	77.4%

	Post	Pre (OFS)
# Events	11	19
HR (95% CI)	1.79 (0.85–3.76), p=0.12	
5-yr estimate	96.5%	93.8%
10-yr estimate	89.6%	84.4%

Fig. 3. Survival analysis of patients with adjuvant chemoendocrine therapy. (a) iDFS of patients with adjuvant chemoendocrine therapy. (b) DRFS of patients with adjuvant chemoendocrine therapy. (c) After PSM, iDFS of patients with adjuvant chemoendocrine therapy. (d) After PSM, DRFS of patients with adjuvant chemoendocrine therapy.

An adjuvant chemotherapy benefit was observed in intermediate genomic risk, lymph node-negative, and all lymph node-positive PRE patients in the TAILORx and RxPONDER studies. After these publications, there was a big debate on whether OFS could replace adjuvant chemotherapy in these patients, as it was unclear whether the chemotherapy benefit was due to the ovarian suppression effects promoted by chemotherapy. In the National Comprehensive Cancer Network (NCCN) Guidelines V4.2024, for PRE women with pN0 and recurrence score

16–25, adjuvant endocrine therapy±OFS is recommended instead of adjuvant chemotherapy. For pN1, adjuvant endocrine therapy plus OFS was administered. Prospective trials have been conducted to answer this question. The NRG-BR009 ("OFSET") trial evaluated whether adjuvant chemotherapy added to OFS and endocrine therapy is superior to OFS and endocrine therapy alone in improving survival among PRE, patients with early-stage breast cancer having ER+, HER2-negative tumors and a 21-gene recurrence score between 16 and 25 (for pN0) and 0–25 (for pN1) [21]. The INTERSTELLAR trial (KBCSG-25) is a prospective single-arm study ongoing in Korea investigating the survival of node-positive PRE patients with breast cancer who have low genomic risk treated with OFS and endocrine therapy without chemotherapy [22]. Before the results of these prospective clinical trials, our study supports the idea that we should treat PRE patients receiving OFS equivalent to POST patients, such as in the decision to administer adjuvant chemotherapy.

However, this study has some limitations. The retrospective design inherently carries the risk of selection bias, even with the use of PSM. Although PSM was performed to minimize baseline imbalances, some differences between the groups were unavoidable, as complete adjustment for all potential confounders was not possible. This limitation should be considered when interpreting the findings. Additionally, our study focused primarily on patients who underwent OFS, potentially skewing the population towards patients with higher risk. Previous research, such as that by Tevaarwerk et al. [23], has shown that the benefit of OFS is more pronounced in patients with high risk, while patients with lower risk may not derive as much benefit [12,23]. Another limitation is the lack of germline mutation data, particularly BRCA1/2 status, which could provide further insight into treatment responses and long-term outcomes. Emerging evidence suggests that BRCA mutation carriers may have distinct tumor biology and responses to endocrine and chemotherapy. Incorporating germline genetic information—at least within the chemoendocrine therapy cohort—would have strengthened our analysis. However, BRCA testing was not routinely performed for all patients in this study; thus, these data were unavailable for inclusion. Future studies should consider integrating germline genetic profiling to better understand its impact on treatment decisions and outcomes. Additionally, a longer follow-up is necessary to assess the impact of OFS on long-term survival, quality of life, and potential late recurrence, particularly in the context of hormone receptor-positive disease, which can recur many years after the initial treatment.

5. Conclusion

In conclusion, this study demonstrated that PRE patients with ER-positive and HER2-negative breast cancer who received OFS achieved iDFS and DRFS outcomes comparable to those of POST women, irrespective of chemotherapy administration. These findings suggest that PRE women receiving OFS may have the same prognosis as POST women and could be treated using the same strategy.

CRediT authorship contribution statement

Min Jung Lee: Writing – review & editing, Writing – original draft, Visualization, Validation, Formal analysis, Data curation. **Ji-Jung Jung:** Writing – review & editing, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Jong-Ho Cheun:** Writing – review & editing. **Eunhye Kang:** Writing – review & editing. **Hong-Kyu Kim:** Writing – review & editing. **Han-Byoel Lee:** Writing – review & editing. **Hyeong-Gon Moon:** Writing – review & editing. **Wonshik Han:** Writing – review & editing, Supervision, Conceptualization.

Ethical approval and informed consent

This study was conducted in accordance with the Declaration of Helsinki and comparable ethical standards. Institutional Review Board approval was obtained. The requirement for informed consent was waived for all patient due to the retrospective nature of the study.

Consent to publication

All authors have read the paper and consent to its publication.

Access to data and data analysis

Min Jung Lee and Ji-Jung Jung has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Summary statistical data will be available from Min Jung Lee (jennmjlee@gmail.com) or Ji-Jung Jung (jijung225@gmail.com) on reasonable request after approval of a proposal.

Funding

This work was supported by the Technology Innovation Program (RS-2024-00508422) funded By the Ministry of Trade Industry & Energy (MOTIE, Korea).

Conflicts of interest

Han-Byoel Lee and Wonshik Han report being a member on the board of directors of and holding stock and ownership interests at DCGen, Co., Ltd., not relevant to this study. Other authors declare no competing interests.

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