VOLUME 29 · NUMBER 21 · JULY 20 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Single-Injection Depot Progesterone Before Surgery and Survival in Women With Operable Breast Cancer: A Randomized Controlled Trial

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Submitted October 13, 2010; accepted April 11, 2011; published online ahead of print at www.jco.org on June 13, 2011.

Supported in part by a grant from the Department of Science and Technology, Government of India.

Presented in part at the 37th Annual San Antonio Breast Cancer Symposium, December 9 to 13, 2009, San Antonio, TX.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

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0732-183X/11/2921-2845/$20.00

DOI: 10.1200/JCO.2010.33.0738

## ABSTRACT

### Purpose
Many nonrandomized studies have suggested better outcome for patients with breast cancer who undergo surgery during the luteal (progestogenic) phase of their menstrual cycle, but this is controversial. We investigated the effect of a single preoperative injection of hydroxyprogesterone in women with operable breast cancer (OBC) in a randomized controlled trial (ClinicalTrials.gov identifier, NCT00123669).

### Patients and Methods
One thousand patients with OBC were randomly assigned to receive surgery or an intramuscular injection of depot hydroxyprogesterone 500 mg 5 to 14 days before surgery. Primary and secondary end points were disease-free survival (DFS) and overall survival (OS), respectively. An analysis by axillary lymph node status was preplanned.

### Results
At a median follow-up of 65 months among 976 eligible patients, 273 recurrences and 202 deaths were recorded. In the progesterone group versus control group, 5-year DFS and OS rates were 73.9% *v* 70.2% (hazard ratio [HR], 0.87; 95% CI, 0.68 to 1.09; $P = .23$) and 80.2% *v* 78.4% (HR, 0.92; 95% CI, 0.69 to 1.21; $P = .53$), respectively. In 471 node-positive patients, the 5-year DFS and OS rates in the progesterone group versus control group were 65.3% *v* 54.7% (HR, 0.72; 95% CI, 0.54 to 0.97; $P = .02$) and 75.7% *v* 66.8% (HR, 0.70; 95% CI, 0.49 to 0.99; $P = .04$), respectively. In multivariate analysis, DFS was significantly improved with progesterone in node-positive patients (adjusted HR, 0.71; 95% CI, 0.53 to 0.95; $P = .02$), whereas there was no significant effect in node-negative patients ($P$ for interaction = .04).

### Conclusion
A single injection of hydroxyprogesterone before surgery did not improve outcomes in all women with OBC. This intervention showed significant improvement in node-positive women that may be considered hypothesis generating. If replicated in other studies, this could be a simple and inexpensive intervention, especially in developing countries where the incidence of lymph node metastasis is high.

*J Clin Oncol 29:2845-2851. © 2011 by American Society of Clinical Oncology*

## INTRODUCTION

Timing of surgery during the menstrual cycle and its impact on long-term survival in breast cancer were first investigated by Hrushesky et al,[1] who hypothesized that events relating to ovulation and menstruation at the time of removal of the primary tumor can influence therapeutic outcome.[2] Their report on 44 patients showed differences in the incidence of distant metastasis when surgery was performed in the periovulatory versus perimenstrual phases of the menstrual cycle.[1] The hypothesis was later refined by others[3] who proposed that the presence of unopposed estrogen at the time of surgery may favor development of metastasis, whereas progesterone would counteract such an effect. A retrospective analysis of 324 patients[3] showed that surgery performed during the follicular phase (unopposed estrogen) resulted in a 10-year overall survival (OS) rate of 40% compared with 70% in patients who received surgery in the luteal phase (estrogenic effect opposed by progesterone). In this study, progesterone levels were available in a subset of patients, and the presence of high levels of progesterone was associated

with an improvement in OS in the lymph node–positive subgroup.[4] Subsequently, a meta-analysis[5] of 37 nonrandomized studies showed better survival in patients who underwent surgery during the luteal phase versus the follicular phase. A combined analysis of three studies[5] that measured circulating progesterone levels at the time of surgery showed an improvement in survival in patients with node-positive disease who had progesterone levels greater than 1.5 ng/mL of serum (hazard ratio [HR], 0.46; 95% CI, 0.29 to 0.74; $P < .001$). However, three subsequent prospective observational studies[6-8] that measured circulating progesterone levels at the time of surgery did not find any difference in survival between the two menstrual groups. However, the effect in patients with axillary lymph node metastasis was not evaluated in two of these studies.[6,7] Thus, the issue remains controversial.[9,10]

Here we report the first prospective randomized controlled trial on timing of surgery in relation to the effect of hormonal milieu on survival. We compare the effect of a pharmacologically induced progestogenic environment versus natural hormonal milieu at the time of surgery in patients with OBC.

## PATIENTS AND METHODS

### Patients

The trial was conducted at a single tertiary cancer center in India. Eligible patients were those with OBC, defined as clinical stage T1 to T3 (with the primary tumor ≤ 6 cm in maximum size), N0 to N1, with no evidence of metastatic disease and no surgical intervention other than fine-needle aspiration cytology or core biopsy. Although previous retrospective studies of timing of surgery were done in premenopausal women, we decided to include pre- and postmenopausal women. It was felt that the latter group with an unopposed estrogenic milieu, albeit of a lower magnitude, would allow assessment of a progestogenic action unconfounded by the presence of endogenous progesterone. The patients provided written informed consent that was approved by the institutional review board.

### Treatment Plan

In the majority of patients, the diagnosis of breast cancer was confirmed preoperatively by fine-needle aspiration cytology. When the clinical suspicion of malignancy was strong, frozen section evaluation followed by definitive surgery was allowed. All patients were planned to undergo standard surgery, and the choice of breast conservation or mastectomy was left to the discretion of the treating surgeon and the patient. The decision on the type of surgery (breast conservation or mastectomy) was made either before or after random assignment. Each surgeon's contribution toward type of surgery and arm of random assignment was similar. Patients in the experimental arm received an intramuscular injection of depot hydroxyprogesterone 500 mg 5 to 15 days before surgery. This interval was determined based on the fact that the half-life of depot hydroxyprogesterone is 15 days. This dose of injected progesterone achieves a blood level of the hormone that is much higher than the physiologic peak achieved during the luteal phase of the natural menstrual cycle.[11] If surgery could not be performed within 15 days after receiving the injection of hydroxyprogesterone, patients were given another injection of the same drug. Patients in the control arm underwent surgery without receiving hydroxyprogesterone.

After surgery, patients received adjuvant treatment according to standard guidelines prevalent during the trial period. Adjuvant chemotherapy regimens included intravenous cyclophosphamide 600 mg/m$^2$, methotrexate 40 mg/m$^2$, and fluorouracil 600 mg/m$^2$ (CMF), all given on days 1 and 8 and repeated every 28 days, or cyclophosphamide 500 mg/m$^2$, doxorubicin 50 mg/m$^2$ or epirubicin 75 mg/m$^2$, and fluorouracil 500 mg/m$^2$ (CAF/CEF), all repeated every 21 days. CMF was the standard of care in the initial part of the study; the practice changed after 2000 to include anthracyclines in the adjuvant chemotherapy protocol (CAF/CEF). After the last cycle of chemotherapy, patients with estrogen receptor (ER) –positive and/or progesterone receptor (PgR) –positive tumors received adjuvant hormonal therapy, which could be either tamoxifen 20 mg/d for 5 years or, in some postmenopausal patients, aromatase inhibitors for the same duration. In the earlier years (1997 to 2000), all postmenopausal women received tamoxifen irrespective of hormone receptor status. No patient received adjuvant trastuzumab. All patients who underwent breast conservation received standard radiation therapy after chemotherapy. The criteria for postmastectomy radiotherapy were pathologic tumor size greater than 5 cm and/or more than three metastatic axillary lymph

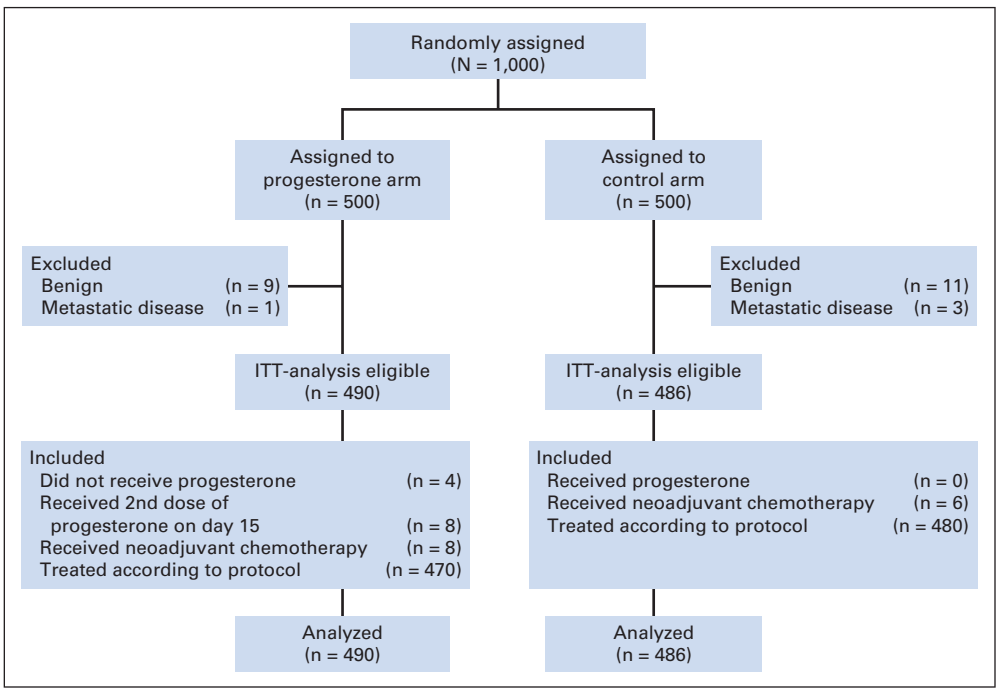


**Fig 1.** Trial profile. Data for the number of patients screened for eligibility were not recorded. ITT, intent to treat.

  

nodes. For the purpose of this report, the term lymph node metastasis indicates patients with evidence of invasive breast cancer in the surgically removed axillary lymph nodes.

On completion of the primary therapy, patients were observed at 6-month intervals with clinical examination. Physicians who performed the follow-up were not blinded to the random assignment arms. Mammography was performed every 18 to 24 months. Metastatic work-up was advised during follow-up only in patients with symptoms or signs of recurrence. Patients with recurrent disease were treated with appropriate local and/or systemic therapies.

**Table 1.** Patient Clinical Characteristics

| Characteristic | Progesterone Arm (n = 490) No. of Patients | % | Control Arm (n = 486) No. of Patients | % |
|---|---|---|---|---|
| Median age, years | 47 | | 46 | |
| Menopausal status | | | | |
| Premenopausal | 263 | 53.7 | 264 | 54.3 |
| Postmenopausal | 227 | 46.3 | 222 | 45.7 |
| Clinical tumor size, cm | | | | |
| ≤ 2 | 99 | 20.2 | 100 | 20.6 |
| > 2.0 to ≤ 5.0 | 371 | 75.7 | 365 | 75.1 |
| > 5.0 | 20 | 4.1 | 21 | 4.3 |
| Median | 3.0 | | 3.0 | |
| Median pathologic tumor size, cm | 3.0 | | 3.0 | |
| Diagnosis | | | | |
| Fine-needle aspiration | 385 | 78.6 | 392 | 80.7 |
| Frozen section | 78 | 15.9 | 81 | 16.7 |
| Other | 27 | 1.8 | 13 | 1.4 |
| Surgery | | | | |
| Mastectomy | 177 | 36.1 | 176 | 36.2 |
| Breast conservation | 313 | 63.9 | 310 | 63.8 |
| Lymph nodes | | | | |
| Negative | 236 | 48.2 | 245 | 50.4 |
| Positive | 239 | 48.8 | 232 | 47.7 |
| Not known | 15 | 3.0 | 9 | 1.9 |
| Median No. of positive nodes | 2.0 | | 2.5 | |
| ER/PgR status | | | | |
| Positive | 238 | 48.6 | 252 | 51.9 |
| Negative | 223 | 45.5 | 215 | 44.2 |
| Not known | 29 | 5.9 | 19 | 3.9 |
| HER2/*neu* status | | | | |
| Negative | 312 | 63.7 | 324 | 66.6 |
| Positive | 72 | 14.7 | 66 | 13.6 |
| Not known | 106 | 21.6 | 96 | 19.8 |
| Chemotherapy | | | | |
| CMF | 97 | 19.8 | 102 | 21.0 |
| CAF or CEF | 278 | 56.7 | 285 | 58.6 |
| Not given | 115 | 23.5 | 99 | 20.4 |
| Hormonal therapy | | | | |
| TAM only | 215 | 43.8 | 234 | 48.1 |
| AI | 7 | 1.4 | 8 | 1.6 |
| TAM + AI | 72 | 14.7 | 59 | 11.8 |
| None | 196 | 40.0 | 185 | 38.0 |
| Adjuvant RT | | | | |
| After mastectomy | 47 | 9.6 | 44 | 9.0 |
| After breast conservation | 292 | 59.6 | 291 | 59.9 |
| Not given | 151 | 30.8 | 151 | 31.1 |

Abbreviations: AI, aromatase inhibitor; CAF, cyclophosphamide, doxorubicin, and fluorouracil; CEF, cyclophosphamide, epirubicin, and fluorouracil; CMF, cyclophosphamide, methotrexate, and fluorouracil; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor; RT, radiotherapy; TAM, tamoxifen.

### *Study Design and Statistical Analysis*

The study was planned as a randomized controlled trial to compare preoperative administration of hydroxyprogesterone versus no preoperative treatment in women with OBC (Fig 1). The primary end point of the study was disease-free survival (DFS) in all patients, defined as the time from random assignment to recurrence of disease at local (invasive cancer), regional, or distant sites or death from any cause. Contralateral breast cancer including ductal carcinoma in situ and second primary cancers were documented but not considered as end points. The secondary end points were OS, defined as the time from random assignment to death as a result of any cause, in all patients and DFS and OS in patients with axillary lymph node metastasis.

Using a group sequential strategy,[12] a sample size of 1,000 was considered adequate to detect an absolute increase in DFS from 65% in the control arm to 75% in the treatment arm with 80% power and $\alpha = .05$. Because earlier retrospective studies had reported a benefit of luteal phase surgery largely in node-positive patients, a survival analysis was preplanned in this subgroup. To allow for preplanned analyses in lymph node–positive patients at the interim and final assessments, the sample size was increased from 660 to 1,000, assuming a lymph node positivity rate of approximately 50% in our patients. The interim and final analyses were planned at 250 and 400 events, respectively. The larger sample size would also account for 5% of patients being lost to follow-up. The study was reviewed in 2001 and 2004 for quality of conduct and

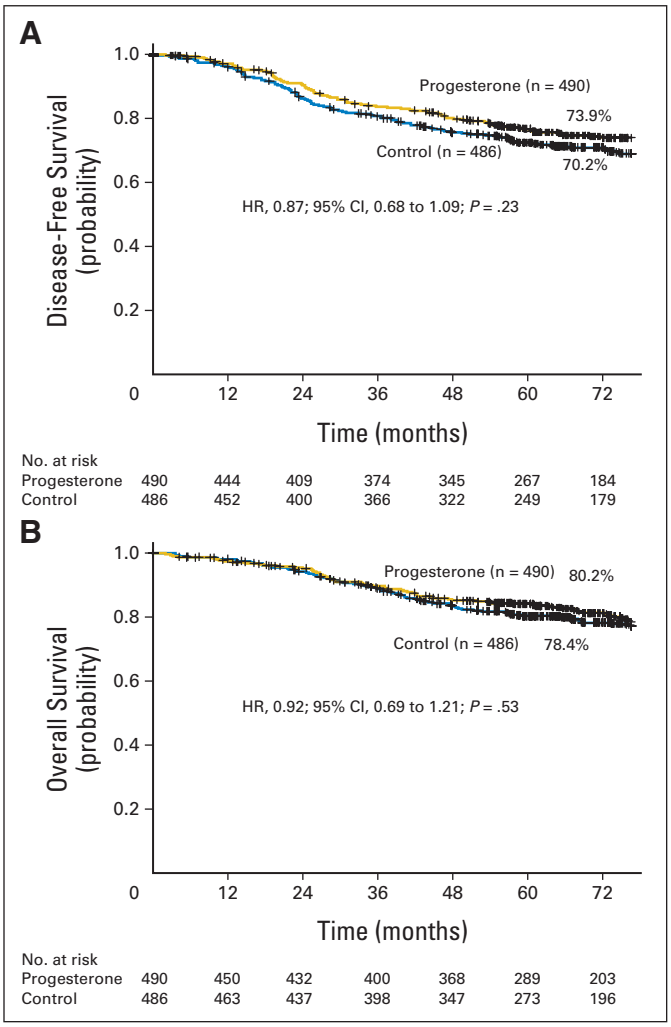


**Fig 2.** Kaplan-Meier estimates of (A) 5-year disease-free survival and (B) 5-year overall survival and the hazard ratios (HRs; with 95% CIs and *P* values) for all patients assigned to receive a single injection of depot hydroxyprogesterone before surgery compared with patients assigned to only surgery.

data management under the guidance of an external data monitoring and safety committee.

Patients were stratified by menopausal status (premenopausal *v* postmenopausal) and clinical tumor size (< 2, 2 to 5, and > 5 cm). Random assignment lists were prepared using computer-generated permuted blocks of four or six varying randomly for each strata. Concealed random assignment was administered telephonically through a central office.

The primary analysis population included all randomly assigned patients with pathologically confirmed breast cancer with no evidence of metastatic disease. This included all patients who received the treatment as per protocol and those who did not receive progesterone in the intervention arm, those who received progesterone in the control arm, and those who received neoadjuvant chemotherapy. All such patients were analyzed within the original randomly assigned arm as per the intent-to-treat principle. Survival analysis was carried out using the Kaplan-Meier method. The univariate analysis of important prognostic factors for DFS was performed using the log-rank test. The multivariate model included all of these variables, entered as categorical values, in a Cox proportional hazards model. The test of interaction using the difference in the log likelihood ratio for treatment effect was performed for menopausal status, tumor size, nodal status, ER/PgR status, and human epidermal growth factor receptor 2 (HER2/*neu*) status. If the test of interaction was positive, Cox analysis was performed within that subgroup. The trial data were analyzed using SPSS version 14.0 (SPSS, Chicago, IL).

## RESULTS

The study was initiated in October 1997 and completed accrual of 1,000 women in December 2004. The follow-up was completed up to April 30, 2009, for this analysis. Five hundred patients were randomly assigned to each arm. As specified in the protocol, an additional dose of hydroxyprogesterone 250 mg had to be given to eight patients in the treatment arm because their surgery was delayed for more than 14 days after the first injection of the study drug. Twenty patients with strong clinical suspicion of malignancy turned out to have benign

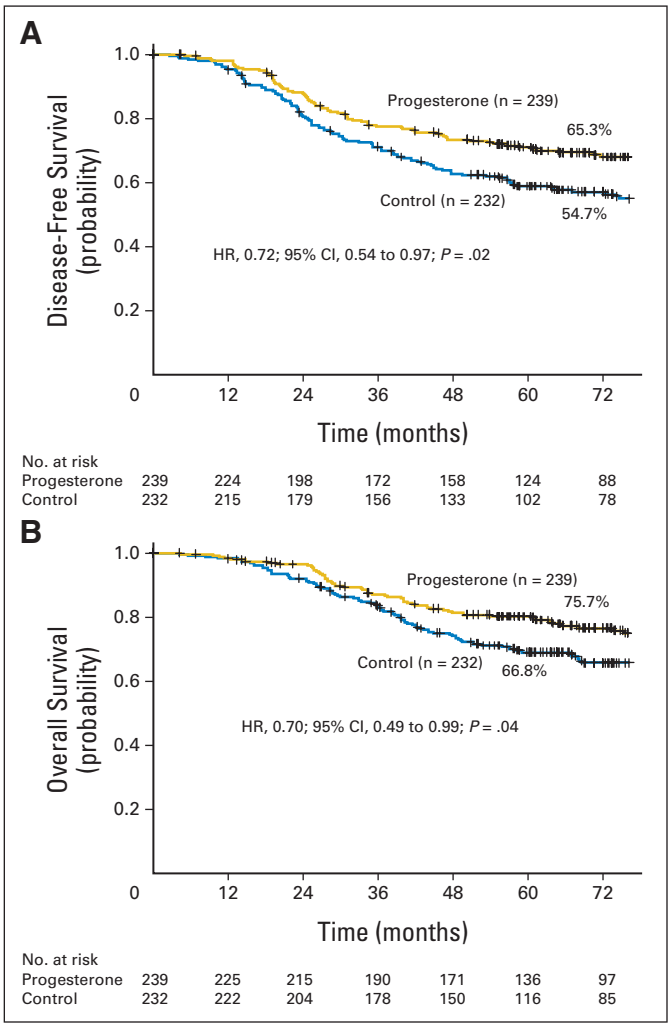


**Fig 3.** Kaplan-Meier estimates of (A) 5-year disease-free survival and (B) 5-year overall survival and the hazard ratios (HRs; with 95% CIs and *P* values) for the patients with lymph node metastases assigned to receive a single injection of depot hydroxyprogesterone before surgery compared with patients assigned to only surgery.

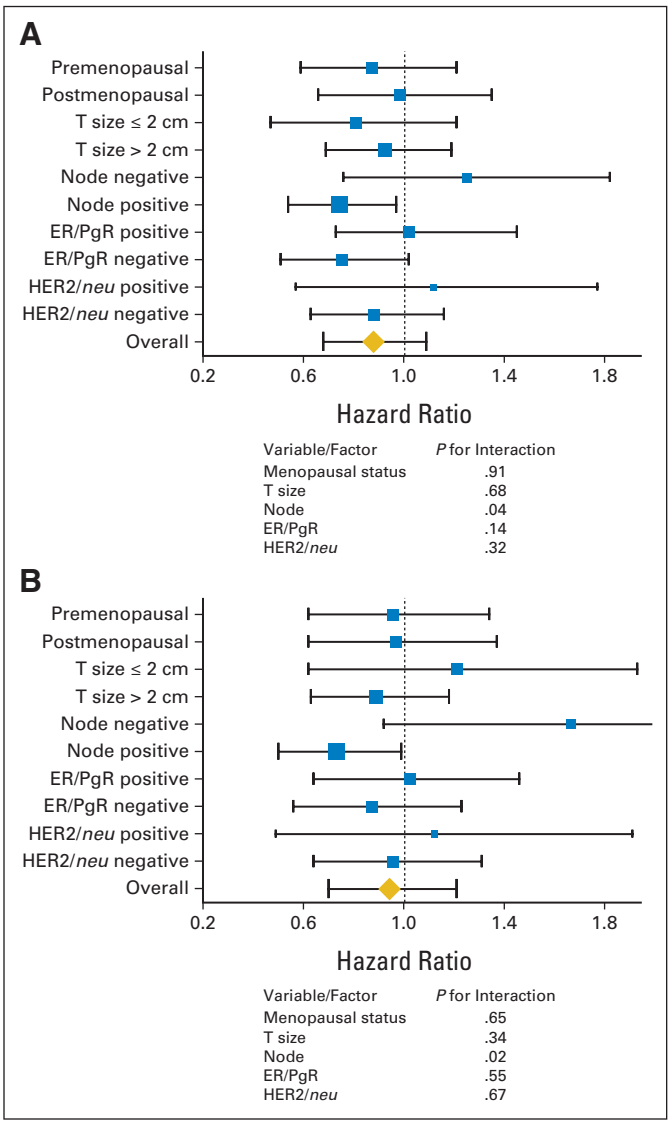


**Fig 4.** Forest plots of (A) disease-free survival and (B) overall survival depicting post hoc (except nodal status) subset analyses. The hazard ratios (HRs; with 95% CIs) for the patients assigned to primary hydroxyprogesterone before surgery, as compared with only surgery, were obtained from the unadjusted Cox model. The dashed vertical line denotes an HR of 1.00, which is the null hypothesis value. The size of squares is not proportional to the number of events in the subgroups. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor; T, tumor.

  

**Table 2.** Univariate Analysis of Prognostic Factors for DFS and OS

| Variable | DFS | | | OS | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *P* | HR | 95% CI | *P* |
| Menopausal status (pre *v* post) | 0.98 | 0.77 to 1.24 | .85 | 1.17 | 0.89 to 1.54 | .26 |
| Tumor size (> 2 v ≤ 2 cm) | 1.09 | 0.83 to 1.43 | .54 | 1.28 | 0.93 to 1.78 | .14 |
| Lymph node positive | 2.70 | 2.08 to 3.50 | < .001 | 2.47 | 1.83 to 3.33 | < .001 |
| Preoperative depot progesterone | 0.87 | 0.68 to 1.10 | .23 | 0.92 | 0.70 to 1.21 | .53 |
| ER or PgR positive | 0.80 | 0.62 to 1.01 | .06 | 0.76 | 0.57 to 1.00 | .054 |

Abbreviations: ER, estrogen receptor; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; PgR, progesterone receptor.

breast disease on frozen section evaluation. Four patients developed evidence of metastatic disease after random assignment before undergoing surgery. The final analysis was performed on 976 patients after excluding these 24 patients (Fig 1). A sensitivity analysis revealed no difference in the results when patients with protocol deviations (n = 24) were included in the analysis (data not shown).

The 976 patients include 18 patients with protocol violations who were analyzed as per their random assignment. Six patients in the control arm and eight in the progesterone arm received neoadjuvant chemotherapy and had their surgery delayed. An additional four patients who were randomly assigned to the progesterone arm did not receive this treatment. The patients lost to follow-up in the two arms are similar (4% in the control arm and 3.6% in the progesterone arm). The two arms are well matched with respect to age, tumor size, lymph node status, hormone receptor status, HER2/*neu* status, and type of surgery (Table 1). Similar numbers of patients underwent frozen section followed by immediate definitive surgery in the control and experimental arms (16.7% and 15.9%, respectively). The use of adjuvant hormonal therapy and radiation was similar in the two arms. The use of CMF and CAF/CEF chemotherapy was similar in the two arms, as was the delivered dose-intensity (data not shown). There were no adverse events reported in relation to injection of hydroxyprogesterone, and there were no postoperative deaths.

At a median follow-up of 65 months, 273 recurrences and 202 deaths were documented. There were 128 recurrences in the progesterone arm and 145 in the control arm. The 5-year DFS rate was 73.9% in the progesterone arm compared with 70.2% in the control arm (HR, 0.87; 95% CI, 0.68 to 1.09; $P = .23$; Fig 2A). The 5-year OS rates were 80.2% and 78.4% in progesterone and control arms, respectively (HR, 0.92; 95% CI, 0.69 to 1.21; $P = .53$; Fig 2B). Thus, there was no statistically significant effect of preoperative hydroxyprogesterone in the entire study population.

Among women with positive axillary lymph nodes, there were 83 and 105 recurrences in the progesterone and control arms, respectively. In a prespecified analysis in these patients (n = 471), the 5-year DFS was 65.3% in the progesterone arm and 54.7% in the control arm (HR, 0.72; 95% CI, 0.54 to 0.97; $P = .02$; Fig 3A). The 5-year OS in node-positive patients was 75.7% in the progesterone arm and 66.8% in the control arm (HR, 0.70; 95% CI, 0.49 to 0.99; $P = .04$; Fig 3B). There was no statistically significant difference in the 5-year DFS and OS rates between the progesterone and control arms in node-negative patients (Appendix Figs A1A and A1B, online only). The effects of preoperative progesterone on survival differed according to axillary nodal status (interaction, $P = .04$ for DFS and $P = .02$ for OS). In a post hoc analysis, the effects of preoperative progesterone did not differ significantly according to menopausal status, tumor size, hormone receptor status, or HER2/*neu* status. (Figs 4A and 4B)

The univariate effect of prognostic factors is shown in Table 2. Only lymph node status significantly impacted the 5-year DFS and OS. A Cox proportional hazards analysis for DFS and OS was performed separately for node-negative and node-positive patients because the test of interaction between this covariate and progesterone effect was positive in the entire study population (Fig 4A and Appendix Fig A1). In node-positive patients, the HR for DFS for preoperative progesterone, adjusted for menopausal status, tumor size, and ER/PgR status, was 0.71 (95% CI, 0.53 to 0.95), whereas in node-negative patients, it was 1.21 (95% CI, 0.78 to 1.89; Table 3). In node-positive patients, the HR for OS for preoperative progesterone, adjusted for menopausal status, tumor size, and ER/PgR status, was 0.67 (95% CI, 0.47 to 0.95), whereas in node-negative patients, it was 1.45 (95% CI, 0.87 to 2.42; Table 3). Table 4 lists data for different levels of node positivity in the two arms.

## DISCUSSION

We have reported the results of a prospective randomized controlled trial that evaluated the effect of an artificially induced progestogenic milieu at the time of surgery on outcome in women with OBC. Preoperative hydroxyprogesterone showed an effect on survival that failed to reach statistical significance in the overall study population. However, a preplanned analysis in patients with node-positive disease showed significant absolute improvements of 10.6% in 5-year DFS and 8.9% in 5-year OS in favor of the progesterone arm. There was no statistically significant effect of progesterone in node-negative patients. Our study supports the hypothesis that events at the time of

**Table 3.** Adjusted* HRs for Preoperative Progesterone for DFS and OS Stratified by Lymph Node Status

| Variable | Lymph Node Negative | | | Lymph Node Positive | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *P* | HR | 95% CI | *P* |
| DFS | 1.21 | 0.78 to 1.89 | .41 | 0.71 | 0.53 to 0.95 | .02 |
| OS | 1.45 | 0.87 to 2.42 | .16 | 0.67 | 0.47 to 0.95 | .03 |

NOTE. The test of interaction between nodal status and treatment is significant for both DFS ($P = .04$) and OS ($P = .01$) (prespecified).

Abbreviations: DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

*Adjusted for menopausal status, tumor size, and hormone receptor status.



 

**Table 4.** Data for Different Levels of Node Positivity in the Two Arms

| Parameter | Progesterone Arm (n = 475) | | Control Arm (n = 477) | |
|---|---|---|---|---|
| | No. of Patients | % | No. of Patients | % |
| Node negative | 236 | 49.7 | 245 | 51.4 |
| 1-3 nodes positive | 148 | 31.2 | 135 | 28.3 |
| ≥ 4 nodes positive | 91 | 19.1 | 97 | 20.3 |

surgery can influence treatment outcome in breast cancer[2,5,13] and raises the possibility that these events can be favorably modulated by injectable preparation of progesterone before surgery. The biologic underpinning of the events at the time of surgery could be either dissemination of cancer cells during surgery[13,14] or autonomy bestowed on pre-existing micrometastases by the act of removal of the primary tumor.[15]

The beneficial effect of progesterone was evident in node-positive patients in our study. These results are consistent with those reported by others[3,16] who observed, in retrospective analyses, that the beneficial effect of surgery during the luteal phase was largely confined to the node-positive subgroup. These findings may have two explanations. The first is statistical. The higher event rate (69% of recurrences) in the node-positive subgroup allowed the detection of a beneficial effect of progesterone in these patients. The second explanation could be that hematogenous dissemination of cancer cells during surgery is facilitated by blocked lymph nodes, which are known to raise interstitial pressure and adversely affect survival.[17] The opening up of lymphaticovenous communications in such high-pressure systems has been documented,[18] allowing easy egress of tumor cells into the venous system. The potential inhibitory effect of progesterone on surgical dissemination would thus be manifested in node-positive patients.

The mechanisms by which progesterone exerts its biologic effects are complex. One of the explanations for these findings could be dissemination of tumor cells during surgical handling facilitated by an estrogenic milieu and prevented by progesterone. Progesterone mediates some of its actions by counteracting the biologic effects of estrogen.[19,20] The latter facilitates cell dehiscence by upregulating proteases[21,22] and inhibiting the effects of E-cadherin.[23] This mechanism is known to affect many epithelial cell types, such as endometrial and cervical, wherein the cellularity of smears obtained during the follicular phase exceeds that obtained during the luteal phase.[24] Thus, these actions of estrogen[21-24] might facilitate tumor cell dissemination during surgery.[25] The cells detached under the influence of estrogen may also have better growth potential in an estrogenic milieu.[26,27] An immunologic mechanism in this context could be the suppression of natural killer cell activity during the estrogenic phase, producing a permissive environment for establishment of micrometastases.[28] Progestins, however, increase cytotoxic T cells and reduce FOXP3-expressing regulatory T cells,[29] thus preventing successful nestling of micrometastases.

The effect of progesterone was not confined to hormone receptor–positive patients, which is somewhat counterintuitive but consistent with previous reports.[30] An exploratory post hoc analysis in our study suggests that the beneficial effect of progesterone was seen in patients with hormone receptor–negative tumors (Appendix Figs A2A and A2B, online only) and not in those with hormone receptor–positive tumors. However, because the test of interaction between hormone receptor status and progesterone was not significant, this could be a result of chance. Alternatively, progesterone has also been reported to inhibit cell growth and invasiveness,[31] cell detachment,[32] and insulin-like growth factor receptor.[32-34] Some of these effects are known to be independent of hormone receptor expression and could, at least partly, account for the beneficial effects of preoperative progesterone seen in this study.

Our study has some weaknesses. A statistically significant effect is evident only in the node-positive group and not in the entire study population; hence, the findings may be construed as hypothesis generating rather than practice changing. The use of preoperative progesterone was not controlled by placebo and may have led to some biases, including during follow-up evaluations. We did not estimate blood hormone levels in this study, and thus, the degree of elevation of progesterone levels in the treated arm compared with the control arm is unknown. However, the pharmacologic dose of progesterone administered in the treatment arm would have overwhelmed the ambient hormonal milieu. Our study may have underestimated the progesterone effect because some premenopausal patients in the control arm would have been in the luteal phase with high ambient progesterone. Finally, the study was conducted entirely at one hospital, and the findings may need replication in a multicenter setting in patients with high risk of node-positive disease.

Despite these caveats, our study supports the hypothesis that pharmacologic induction of a progestogenic milieu at the time of primary breast cancer surgery may be beneficial in terms of DFS and OS in node-positive patients. Our study also suggests that the preoperative and perioperative period may be a window of opportunity in primary breast cancer for other short-term interventions with the potential to prevent metastasis. Approximately 50% of the 1.1 million annually diagnosed breast cancers worldwide are node positive.[35] If this treatment strategy was to be corroborated in other studies, many lives could be saved at little cost, especially in developing countries where the majority of patients present in relatively late stages.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

## AUTHOR CONTRIBUTIONS

**Conception and design:** Rajendra Badwe
**Administrative support:** Rajendra Badwe, Rohini Hawaldar, Vaibhav Vanmali
**Provision of study materials or patients:** Rajendra Badwe, Vani Parmar, Sudeep Gupta, Rakesh Jalali
**Collection and assembly of data:** Rohini Hawaldar, Vani Parmar, Mandar Nadkarni, Tanuja Shet, Sangeeta Desai, Sudeep Gupta, Rakesh Jalali, Vaibhav Vanmali
**Data analysis and interpretation:** Rajendra Badwe, Rohini Hawaldar, Sudeep Gupta, Rajesh Dikshit, Indraneel Mittra
**Manuscript writing:** All authors
**Final approval of manuscript:** All authors

  

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