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ORIGINAL REPORT

Menstrual Cycle and Surgical Treatment of Breast Cancer: Findings From the NCCTG N9431 Study

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose

For nearly two decades, multiple retrospective reports, small prospective studies, and meta-analyses have arrived at conflicting results regarding the value of timing surgical intervention for breast cancer on the basis of menstrual cycle phase. We present the results of a multi–cooperative group, prospective, observational trial of menstrual cycle phase and outcome after breast cancer surgery, led by the North Central Cancer Treatment Group (NCCTG) in collaboration with the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the International Breast Cancer Study Group (IBCSG).

Patients and Methods

Premenopausal women age 18 to 55 years, who were interviewed for menstrual history and who were surgically treated for stages I to II breast cancer, had serum drawn within 1 day of surgery for estradiol, progesterone, and luteinizing hormone levels. Menstrual history and hormone levels were used to determine menstrual phase: luteal, follicular, and other. Disease-free survival (DFS) and overall survival (OS) rates were determined by Kaplan-Meier method and were compared by using the log-rank test and Cox proportional hazard modeling.

Results

Of 1,118 women initially enrolled, 834 women comprised the study cohort: 230 (28%) in luteal phase; 363 (44%) in follicular phase; and 241 grouped as other. During a median follow-up of 6.6 years, and in analysis that accounted for nodal disease, estrogen receptor status, adjuvant radiation therapy or chemotherapy, neither DFS nor OS differed with respect to menstrual phase. The 5-year DFS rates were 82.7%, 82.1%, and 79.2% for follicular, luteal, or other phases, respectively. Corresponding OS survival rates were 91.9%, 92.2%, and 91.8%, respectively.

Conclusion

When menstrual cycle phases were strictly defined, neither DFS nor OS differed between women who underwent surgery during the follicular phase versus the luteal phase. Nearly 30% of the patients did not meet criteria for either follicular- or luteal-phase categories.

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INTRODUCTION

The concept of timing surgical intervention to treat breast cancer in premenopausal women based on the phase of the menstrual cycle originated with a preliminary communication by Hrushesky et al[1] in 1989. These investigators had found a correlation between estrous stage at primary mammary cancer resection and risk of subsequent pulmonary metastases in mice.[2] They then conducted a retrospective study of 44 premenopausal women, in whom disease recurrence and death were more common when surgery was performed during the perimenstrual interval (ie, menstrual cycle days 0 through 6 and 21 through 36) compared with midcycle (ie, menstrual cycle days 7 through 20). Subsequent studies did not support the same favorable window for surgical treatment during midcycle, as reported by Hrushesky et al.[1]

Follicular- Versus Luteal-Phase Theory

Subsequently, a series of retrospective studies of women who underwent primary breast cancer surgery from the 1970s to early 1990s used last menstrual period (LMP) to determine menstrual cycle phase at time of surgery. Although Badwe et al[3] failed to corroborate the findings of Hrushesky et al, when Badwe et al divided the menstrual cycle into follicular (ie, days 3 through 12 after LMP) and luteal (ie, days 0 through 2 and 13 through 32)

phases, 10-year overall survival (OS) was reduced in women who underwent operation during the follicular phase (54%) compared with the luteal phase (84%). These findings led the Guy's Hospital breast unit staff to schedule surgery at least 12 days after LMP, as they concluded that the disadvantage delay would be outweighed by the potential for long-term benefit. A similar observation was reported by Senie et al[4] from Memorial Sloan-Kettering Cancer Center, in which there was a 10-year recurrence rate of 43% during the follicular phase as opposed to 29% during the luteal phase. In response to the Senie study, Current Opinion in Obstetrics and Gynecology stated, "Few papers produce immediate change in medical practice. This one should! The survival data for women undergoing breast surgery during the luteal phase of the menstrual cycle compared with those undergoing breast surgery during the follicular phase of the menstrual cycle are compelling."[5(p843)]

Veronesi et al[6] found disease-free survival (DFS) in women who underwent operation during follicular phase was significantly decreased relative to women who underwent operation during luteal phase, but the difference was only in women with node-positive disease: 63.3% versus 75.5%, respectively.

In contrast to these reports, numerous reports failed to demonstrate a survival difference according to the Hrushesky breakdown of menstrual cycle relative to breast cancer surgery.[3,4,7,8] Other analyses, which defined the menstrual cycle as follicular (ie, days 1 through 14 after LMP) and luteal (ie, days ≥ 15 after LMP) phases, found no differences in recurrence or survival with respect to the timing of breast cancer surgery in premenopausal women.[9-14] However, a meta-analysis of the 21 published studies before 1994 concluded that the effect of timing of surgery on survival was significant, and its odds reduction was 16% for treatment in the luteal phase.[15]

Within months of the meta-analysis report, Kroman et al[14] reported the largest such study. When using data from 1,635 premenopausal women from 1977 to 1989 collected in the nationwide registry of the Danish Breast Cancer Cooperative Group, the 5-year OS rates were 79% and 80% for surgical intervention during the luteal and follicular phases, respectively.

The inaccuracies inherent in determination of menstrual phase on the basis of LMP combined with conflicting findings on the impact of surgical timing on survival outcome (Tables 1 and 2) led to the search for both retrospective cohorts with preoperative circulating hormone determinations and prospective studies to address the question of the most appropriate time for surgery. Ville[10] gathered such a retrospective cohort and found no difference in DFS or OS with respect to menstrual phase at surgery as determined by circulating levels of estradiol (E2), progesterone (Pg), and luteinizing hormone (LH).

The first prospective study enrolled 360 women who underwent a one-stage surgical procedure,[22] but relapse-free survival (RFS) and OS did not differ by the menstrual cycle phase of surgical intervention. Recently, Thorpe et al[23] reported the 3-year overall survival and DFS rates of a multicenter, prospective study that incorporated both LMP and hormonal data in 256 patients. The timing of surgery in relation to menstrual cycle phase had no significant impact on 3-year survival.

We present here the results of a multi–cooperative group, prospective, observational trial of menstrual cycle phase and outcome after surgery for early-stage breast cancer, led by the North Central Cancer Treatment Group (NCCTG) in collaboration with the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the

Table 2. Studies That Showed No Survival Advantage on the Basis of Phase of Menstrual Cycle

Study	Total No. of Patients	Follow-Up (years)	Menstrual Cycle Determination
Powles[7]	81	11	LMP
Gelber[8]	245	9	LMP
Ville[10]	165		Hormonal
Low[12]	125		
Kroman[14]	1,635	10	LMP
Pujol[22]	360	≤ 7	LMP, hormonal
Thorpe[23]	412	3	Prospective: LMP, hormonal
Nathan[24]	132	≤ 11	LMP
Ville[25]	279	5	LMP
Rageth[26]	217	5.1	LMP
Donegan[27]	97	≤ 10	LMP
Corder[28]	157		LMP
Gnant[29]	385	5	LMP
Wobbes[30]	89	4.1	Hormonal
Milella[31]	248	5	LMP

Abbreviation: LMP, last menstrual period.

Table 1. Luteal-Phase Survival Advantage

Study	Total No. of Patients	Menstrual Cycle Determination	% DFS		Special Circumstances
			Luteal	Follicular	
Badwe[3]	249	LMP	84	54	Node-positive; ER status, no difference
Senie[4]	283	LMP	71	57	
Veronesi[6]	1,175	LMP	75.5	63.3	Node-positive only
Goldhirsch[13]	1,033	LMP	58	53	Node-positive only*
Badwe[16]	150	LMP	68	38	
Badwe[17]	93	Hormone			Hazard ratio, 2.1; follicular (node-positive only)
Saad[18]	96	LMP	72	40	
Holli[19]	267				
Mohr[20]	289				
Cooper[21]	112	LMP	75	45	ER-positive only

Abbreviations: DFS, disease-free survival; LMP, last menstrual period; ER, estrogen receptor.
*% DFS with ER-negative group: luteal, 59; follicular, 42.

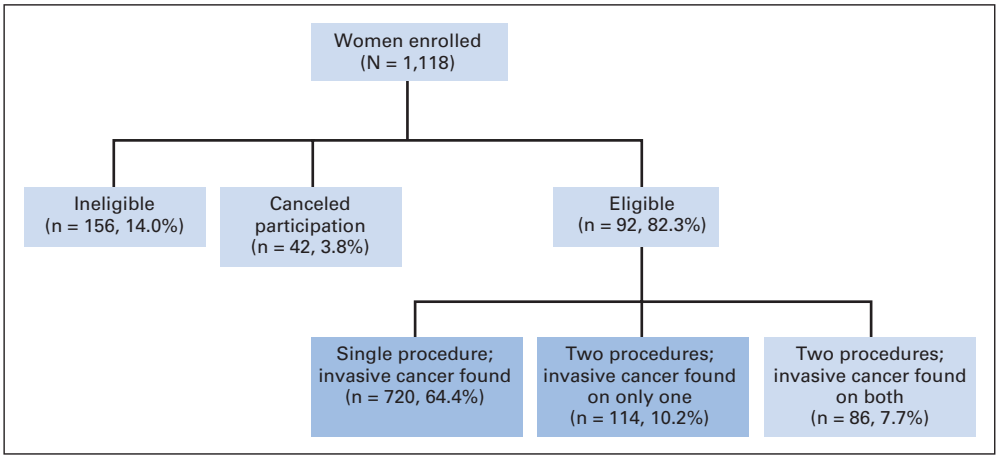

Fig 1. Distribution of patients according to eligibility and single- *v* two-stage operations.

International Breast Cancer Study Group (IBCSG). Menstrual cycle phase was defined by hormone levels and patient menstrual history obtained within 1 day of surgery. Enrollment was limited to women with regular menstrual cycles.

PATIENTS AND METHODS

This prospective, observational, phase III clinical trial was designed to document the proportion of women for whom the menstrual phase at primary breast surgical intervention could be determined by circulating hormone levels and menstrual history and to assess whether DFS differs with respect to menstrual cycle phase (follicular *v* luteal) at the time of primary surgery.

Eligibility

This trial enrolled premenopausal women age 18 to 55 years who had regular menstrual cycles of 21- to 35-days duration and pathologic stages I to II breast cancer, in whom all gross disease—including ductal carcinoma in situ—was surgically removed either in a one-stage or two-stage procedure. Surgical treatment consisted of an open biopsy followed by a mastectomy or breast-conserving surgery with or without sentinel node biopsy and/or axillary nodal dissection. Fine needle aspirates and core or stereotactic needle biopsies were allowed before the definitive procedure. Chemotherapy and/or radiotherapy were allowed in accordance with internationally accepted criteria, as per investigator's discretion. Eligibility required serum be drawn within 1 calendar day of the lumpectomy/mastectomy for women who underwent a one-stage procedure and within 1 calendar day of each stage for women who underwent a two-stage procedure. Exclusion criteria were as follows: oral contraceptive use, lactation within the past 3 months, galactorrhea, neoadjuvant therapy, previous breast cancer, and history of any cancer (except squamous or basal cell skin carcinoma) in which the patient was not disease-free for at least 10 years. This trial was performed after approval by local institutional review boards in accordance with assurances filed with and approved by the US Department of Health and Human Services. Written informed consent was provided by each patient before entry on study.

Patients were observed every 6 months for the first year postregistration and annually for the next 2 to 10 years postregistration for adjuvant therapy information, disease recurrence, and death.

Patients were interviewed at the time of the primary cancer surgery to determine the menstrual history. Blood sampling occurred within 1 day of surgery, and serum samples were shipped frozen to a central laboratory (Mayo Medical Laboratory, Rochester, MN) for E2, Pg, and LH determinations. Serum hormone levels, menstrual cycle length, and day of last menses were used to determine the menstrual phase at which surgery occurred.

Menstrual phase categories were defined as follows: normal luteal phase, serum Pg level $\geq$ 5 ng/mL (with menstrual cycle interval of 21 to 35 days)[32]; normal follicular phase, serum Pg level $\leq$ 3 ng/mL before cycle day 21 (with menstrual cycle interval 21 to 35 days)[32]; anovulation, serum Pg level less than 3 ng/mL after cycle day 21; possible luteal phase, serum Pg between 3 and 5 ng/mL; persistent corpus luteum, serum Pg level greater than 3 ng/mL before cycle day 5; and oligo-ovulation, serum Pg level greater than 3 ng/mL after cycle day 35. For purposes of statistical analyses, primary comparison was between groups of normal luteal phase and normal follicular phase; groups of anovulation through oligo-ovulation were combined into the category of other.

Statistical Design and Analysis

The primary end point of this trial was DFS, which was defined as the time from registration to the recurrence of tumor at any local, regional, or distant location; the detection of a second primary cancer; or death as a result of any cause without documentation of recurrence. Ipsilateral breast tumor recurrences after breast-conserving surgery were considered an event. A secondary end point was OS, which was defined as time from registration to death as a result of any cause.

This study was designed with the assumption that 75% of the patients would have surgery during the follicular phase, the enrollment period would be 5 years, and the follow-up period after the close of enrollment would be 3 years. With a sample size of 804 women, a two-sided $\alpha = .05$ log-rank test would have a power of 82% to detect a 10% difference in the 5-year DFS rate from 67.5% to 77.5% when the follicular group has the poorer DFS, or a power of 86% to detect a 10% difference in the 5-year DFS rate from 67.5% to 77.5% when the luteal group has the poorer DFS. The expected number of events was 218.

For each menstrual cycle group, the distributions of DFS and OS were estimated by using the Kaplan-Meier method. A log-rank test and univariate Cox proportional hazard modeling were used to assess whether the distributions of DFS or OS differed with respect to menstrual cycle phase at surgery or other patient/disease characteristics. For each end point, multivariate Cox modeling was used to obtain a subset of patient/disease characteristics that provided an adequate fit to the data. Residual plots were examined to assess model adequacy. Then, a likelihood ratio test was used to assess whether menstrual cycle phase at surgery made a significant contribution to this model. Interaction between estrogen receptor status (ER) and menstrual cycle phase at surgery was assessed.

RESULTS

Study Cohort

From July 1996 through December 2001, 1,118 (Fig 1) women were enrolled onto this trial by the NSABP (69.3%), NCCTG (16.5%), and IBCSG (14.2%). One hundred fifty-six women (14.0%) were

declared ineligible because of pathology findings that disease was not stages I to II (n = 58), blood was not drawn per protocol (n = 46), residual disease remained after final surgery (n = 18), length of menstrual cycle was not 21 to 35 days or was not known (n = 15), chemotherapy or hormonal therapy was administered before first or second operative procedure (n = 15), oral contraceptive use occurred within 3 months of study entry (n = 3), and prior hysterectomy had been performed (n = 1). Seven women (0.6%) signed a consent form but refused to participate before the first or second operative procedure. An additional 35 patients (3.1%) were administratively canceled from additional participation because their blood specimens were improperly drawn, lost in transit, grossly hemolyzed, or thawed during shipment. Of the remaining 920 women, 720 women underwent a single surgical procedure in which cancer was detected, and 114 women underwent two surgical procedures in which cancer was identified at only one procedure. These 834 women comprised our study cohort.

Menstrual Phase

At the time of the surgical procedure, 230 women (28%) were classified as normal luteal phase; 363 women (44%) were classified as normal follicular phase, and the remaining 241 patients were grouped as other. Of those in the other group, 142 women (17%) were anovulatory, 71 women (9%) had a questionable luteal phase, 15 women (2%) were oligo-ovulatory, eight women (1%) had a persistent corpus luteum, and five women (1%) had inconsistent or contradictory information so that they could not be classified. Patient, disease, and treatment characteristics were well balanced between groups on the basis of menstrual cycle phase (Table 3).

Clinical Outcomes

There have been 177 patients who developed recurrent disease or a second primary or who died without documentation of recurrence. First events included the following: local recurrence (n = 54), distant metastasis (n = 76), contralateral breast disease (n = 16), other second primary (n = 17), multiple disease event (n = 7), and death without disease recurrence (n = 7; Table 4). The estimated 5-year DFS rate was 81.5% (95% CI, 78.8% to 84.3%). There were 87 deaths, and reported causes of death included local/distant disease (n = 72), second primary disease (n = 5), other causes (n = 6), and unknown causes (n = 4). The median length of follow-up among the 747 patients known to be alive was 6.6 years (range, 1 day to 10.0 years). The estimated 5-year OS rate was 92.0% (95% CI, 90.1% to 93.9%).

Menstrual Phase at Surgery and Clinical Outcome

DFS or OS in all patients did not differ with respect to menstrual phase at surgery (follicular *v* luteal *v* indeterminate: log-rank $P = .639$ and .456, respectively.) The estimated 5-year DFS rates were 82.7% (95% CI, 78.7% to 86.8%), 82.1% (95% CI, 77.1% to 87.5%), and 79.2% (95% CI, 73.9% to 84.7%) among women who had surgery during the follicular, luteal, or indeterminate phases, respectively.

The estimated 5-year OS rates were 91.9% (95% CI, 89.1% to 94.8%), 92.2% (95% CI, 88.7% to 95.9%), and 91.8% (95% CI, 88.2% to 95.5%) among women who had surgery during the follicular, luteal, or indeterminate phases, respectively.

Table 3. Patient Demographic and Disease and Treatment Clinical Characteristics

Characteristic	% of Patients by Menstrual Phase		
	Luteal (n = 230)	Follicular (n = 363)	Other (n = 241)
Age at surgery, years			
Median	42	42	42
Range	28-52	22-54	23-53
Ethnicity			
White	82.2	82.6	84.7
African American	9.1	8.3	9.5
Asian	2.6	4.1	1.2
Hispanic	2.6	3.3	3.3
Native Hawaiian/ Pacific Islander	0.4	0.6	0
Other	0.9	0.8	1.2
Not provided	2.2	0.8	0
Surgical procedure			
One-step	87.0	85.4	87.1
Two-step	13.0	14.6	12.9
Estrogen receptor status			
Positive	72.6	67.8	70.5
Borderline	0.9	0.6	0.4
Negative	25.7	31.4	28.2
Not done	0.9	0.3	0.8
Histology			
Ductal	90.9	88.2	90.5
Lobular	4.4	6.3	5.4
Other	5.7	5.5	4.1
No. of positive nodes			
Not evaluated	0	1.4	0.8
0	62.2	58.9	58.9
1-3	28.7	30.3	30.3
4-9	6.1	7.2	7.1
≥ 10	3.0	2.2	2.9
T stage			
1	62.6	61.7	55.2
2	36.5	37.7	43.6
3	0.9	0.6	1.3
Adjuvant therapy			
Chemotherapy	73.0	73.3	78.8
Radiation therapy	63.0	69.2	69.7
Hormonal therapy	63.0	55.7	59.3

Outcomes Among Women Who Underwent Surgery During the Follicular or Luteal Phase

DFS time by univariate analysis did not differ between women who underwent surgery during the follicular phase versus the luteal phase (hazard ratio [HR], 0.88; 95% CI, 0.62 to 1.26; log-rank $P = .498$; Fig 2). After analysis accounted for nodal disease, ER status, adjuvant radiation therapy, and adjuvant chemotherapy, menstrual phase at surgery was not associated with DFS (n = 587; adjusted HR [HR_{adj}]; [follicular *v* luteal], 0.83; 95% CI, 0.58 to 1.19; $P = .319$). The HR_{adj} appeared to differ according to ER status (interaction $P_{adj} = .027$; for ER-positive cohort: n = 416; HR_{adj} [follicular *v* luteal], 1.16; 95% CI, 0.72 to 1.87; for ER-negative cohort: n = 171; HR_{adj} [follicular *v* luteal], 0.532; 95% CI, 0.31 to 0.93).

Similarly, survival time by univariate analysis was similar between women who underwent surgery in the follicular phase and

Table 4. Clinical Outcomes According to Menstrual Phase

Outcome	No. of Patients by Menstrual Phase		
	Luteal (n = 230)	Follicular (n = 363)	Other (n = 241)
First event*	52	73	52
Locoregional recurrence	12	26	16
Distant metastases	22	28	26
Contralateral breast disease	10	5	1
Other second primary disease	5	4	8
Multiple disease events	1	6	0
Death without disease recurrence	2	4	1

*Percent of patients with first event by menstrual phase as follows: luteal, 23.6; follicular, 20.1; other, 21.6.

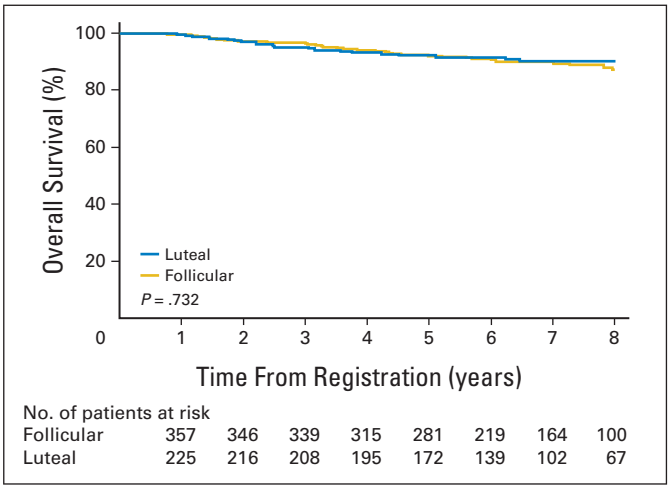

Fig 3. Overall survival of patients who underwent operation during follicular and luteal menstrual phases.

those whose surgery was in the luteal phase (HR [follicular *v* luteal], 1.10; 95% CI, 0.64 to 1.88; log-rank $P = .732$; Fig 3). Moreover, OS did not differ with respect to menstrual phase at surgery after analysis was adjusted for nodal disease and ER tumor status (HR_{adj} [follicular *v* luteal], 1.00; 95% CI, 0.58 to 1.71; $P = .985$).

The interaction between ER status and menstrual phase was not significant for OS (interaction $P_{adj} = .232$; for ER-positive cohort, n = 417; HR_{adj} [follicular *v* luteal], 1.46; 95% CI, 0.68 to 3.16; for ER-negative cohort, n = 173; HR_{adj} [follicular *v* luteal], 0.780; 95% CI, 0.36 to 1.68).

DISCUSSION

In this prospective study of 834 premenopausal women with early-stage breast cancer who had biochemical definition of menstrual cycle phase, neither DFS nor OS differed between women who underwent surgery during the follicular phase compared with the luteal phase after a median follow-up of 6.6 years. Moreover, even after analysis was adjusted for nodal status and ER tumor status, menstrual phase at the time of surgery was not significantly associated with either DFS or OS. Menstrual phase for each patient was defined by the combination of menstrual history obtained at the time of surgery and hormonal values obtained from blood that had been drawn within 1 calendar day of the surgical intervention. Nevertheless, 29.3% of the patients did not meet criteria for either normal follicular- or luteal-phase categories. Notably, as a group, these patients classified in the other category did not differ with respect to DFS or OS from the patients in the normal follicular or luteal phases.

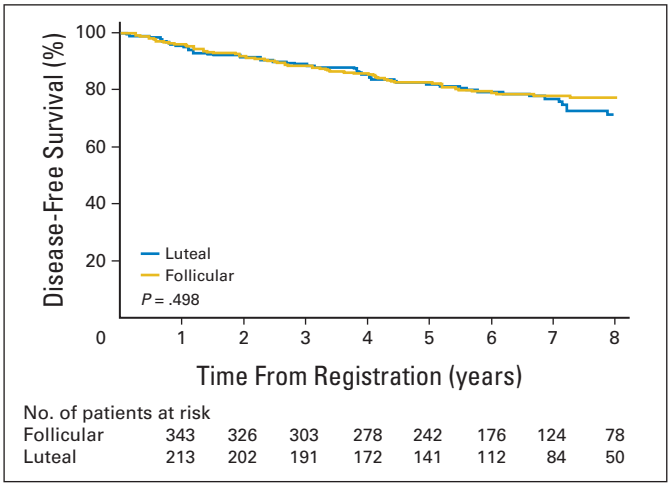

Fig 2. Disease-free survival of patients who underwent operation during follicular and luteal menstrual phases.

Although patients in this study with ER-negative tumors had better outcomes if their operations were performed in the follicular phase, Goldhirsch et al[13] found precisely the opposite—a significantly improved outcome (ie, DFS) for operations during the luteal phase in this subpopulation. This provides additional support that conclusions should be based on the overall findings.

The controversy regarding a possible link between menstrual cycle phase at surgery for breast cancer and outcome has existed for almost 20 years,[1] and the large majority of data are derived from retrospective studies with menstrual cycle phases defined by chart documentation of the LMP. This study is the largest prospective trial to address this question, in which menstrual cycle phase—follicular or luteal—was defined biochemically by hormone levels obtained within 1 day of surgery. Thorpe et al[23] reported 3-year survival data for 256 patients who had hormonal characterization of follicular versus luteal phase at primary breast cancer surgery and saw no difference in outcome with menstrual cycle phase. In contrast to the criteria in this study for categorization of patients into luteal and follicular phases, the Thorpe study used an independent expert to assign the patients. Pujol et al conducted a similar study in 350 women and found no difference in outcome[22] when biochemically determined cycle phase was compared with what would have been assigned on the basis of chart review. Notably, 52% of participants would have been misclassified on the basis of chart dates alone.

Some explanation must be considered to account for the multitude of studies, and even three meta-analyses,[15,33,34] that concluded that patients who underwent operation during the luteal phase had improved survival, with odds reduction of 12% to 16%. Virtually all criticisms of prior retrospective studies have focused on two problems: different definitions of the favorable, luteal phase, timeframe or the

potential inaccuracies in determination of menstrual cycle phase on the basis of LMP, as obtained from review of a patient's clinical records. As is apparent from this study, in which nearly 30% of patients could not be assigned to either menstrual phase despite hormonal levels, misclassification of such a large segment of a study population would certainly lead to discrepancies in findings.

One limitation of this study design was its lack of random assignment. However, at the time of study initiation, there were insufficient data to justify delaying surgical intervention for the sole purpose of randomly assigning patients to surgery on the basis of menstrual cycle phase. Even without random assignment, patient registration onto the study resulted in a fairly even distribution between follicular- versus luteal-phase surgical intervention, given our stringent criteria of normal follicle and luteal phases. Another possible limitation was the allowance of fine-needle aspiration or core needle biopsy for diagnostic purposes. We recognize that perturbation of the tumor occurs with these diagnostic procedures. However, such minimal intervention has not been recognized to alter prognosis and has become common practice (if not standard of care) in present-day breast cancer management. Finally, this study did not dictate the use of adjuvant therapy after surgery. It would have been highly unlikely that we could secure the needed investigator and patient agreement to standardize the approach used for all participants in this trial. Because we captured relevant adjuvant treatment information on all participating patients, we were able to determine that there were no imbalances in the patient group treatments in this regard.

In conclusion, this large, prospective study, which used biochemical definition of menstrual cycle phase, does not confirm a relationship between DFS or OS and timing of surgery on the basis of the menstrual cycle phase of premenopausal women with early-stage breast cancer. It emphasizes the crucial need for such studies to use stringent menstrual information with appropriate hormone determinations to classify the menstrual cycle phase of premenopausal surgical candidates.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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