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Report

Breast cancer and timing of surgery during menstrual cycle: a 5-year analysis of 248 premenopausal women

Michele Milella[1], Cecilia Nisticò[2], Virginia Ferraresi[1], Angela Vaccaro[2], Alessandra Fabi[1], Anna Maria D'Ottavio[2], Claudio Botti[3], Diana Giannarelli[4], Massimo Lopez[5], Enrico Cortesi[6], Carlo Maria Foggi[7], Mauro Antimi[8], Edmondo Terzoli[2], Francesco Cognetti[1], and Paola Papaldo[1]

[1]*Division of Medical Oncology I,* [2]*Service of Complementary Medical Oncology,* [3]*Division of Surgery,* [4]*Department of Biostatistics,* [5]*Division of Medical Oncology II, Regina Elena Cancer Institute;* [6]*Special Service of Oncology, University of Rome "La Sapienza";* [7]*Division of Medical Oncology, Hospital S. Filippo Neri;* [8]*Service of Medical Oncology, Hospital S. Eugenio, Rome, Italy*

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Summary

In the present report, we retrospectively analyzed the impact of the timing of surgery during menstrual cycle on disease-free and overall survival of 248 premenopausal patients with stage I/Il breast cancer who underwent surgery followed by anthracycline-containing adjuvant chemotherapy. With a median follow-up of 5 years, no statistically significant differences were observed in disease-free or overall survival between women operated upon during the follicular (days 0–14) and the luteal (days 15–32) phase of the menstrual cycle. The impact on disease-free and overall survival of lymph-node status, tumor size and hormone receptor expression, but not of the phase of the menstrual cycle at the time of surgery, was confirmed by univariate and multivariate analysis.

However, when combined with hormone receptor status, the phase of the menstrual cycle at the time of surgery proved useful to better define the prognosis of primary breast cancer patients, with significantly longer disease-free and overall survival for patients operated upon during the follicular phase and with positive hormone receptors.

Introduction

Although most of the recognized risk factors of breast cancer suggest the hormone dependency of the disease, the influence of the cyclical variations of estrogens and other hormones during the menstrual cycle on the biological mechanisms of normal breast tissue proliferation as well as of tumor growth and dissemination have not been well characterized. Moreover, the potential effect of cyclical hormone levels on detection, diagnosis and treatment of breast cancer has only recently become a focus of research [1].

The phases of the menstrual cycle are characterized by sizeable hormonal fluctuations. The follicular phase is defined by a preovulatory estrogen peak in the absence of progesterone. During the luteal phase, after ovulation, simultaneous increase of both hormones occur. Researchers studying normal breast tissue have documented the cyclical patterns of DNA synthesis and rates of cell division and cell death [2, 3]. However, the potential influence of the menstrual cycle on breast carcinoma survival was only recently suggested by Hrushesky and colleagues, in both laboratory animals and breast cancer patients [4, 5]. Their study of 41 patients revealed an improved prognosis among women with primary breast surgery between days 7 and 20 of the menstrual cycle (mid-cycle), when compared to the survival of those whose surgery occurred during the perimenstrual interval.

Following this first report, in the last few years, the influence of the timing of surgery with respect to the menstrual phase on disease-free and overall

survival of premenopausal breast cancer patients has been investigated by several authors [1, 6]. Although correlations between hormone profile, immunologic parameters and tumor cell growth characteristics have been evoked, the results of the published studies have been largely conflicting. Moreover, the comparison among different trials is complicated by differences in menstrual cycle division, extent of primary surgery, adjuvant chemotherapy, duration of follow-up and analytic procedures [1, 6].

Objective difficulties in result interpretation notwithstanding, in 1994 Fentiman et al. reported the conclusive data of a meta-analysis of all published studies showing a significant effect of the timing of surgery within the menstrual cycle, with an average odds reduction of 16% for treatment in the luteal phase [7].

On the basis of these findings, we retrospectively analyzed a series of premenopausal breast cancer patients who underwent primary surgery between 1991 and 1994 to further explore the possible prognostic role of the menstrual cycle phase at the moment of tumor excision.

Patients and methods

Patient population

From October 1991 to April 1994, 506 stage I/Il breast cancer patients underwent surgery followed by four courses of adjuvant chemotherapy with epidoxorubicin 120 mg/m^2 i.v. d1 and cyclophosphamide 600 mg/m^2 i.v. d1 every three weeks (EC), in the setting of a randomized multicentric prospective trial, designed to evaluate the impact of the addition of Lonidamine and/or G-CSF to the EC chemotherapy regimen on disease-free and overall survival [8]. Patients were stratified according to the following established prognostic factors: axillary lymph-node status (negative nodes, 1–3, 4–9, ≥ 10 positive nodes), tumor size (≤ 1 cm, 1.1–2.0 cm, 2.1–3.0 cm, > 3.0 cm) and hormone receptor expression, as assessed by immunohistochemistry. After stratification, patients were allocated to one of the following treatment arms: (1) EC (2) EC + Lonidamine (3) EC + G-CSF (4) EC + Lonidamine + G-CSF.

Ascertainment of menstrual status

Each patient was interviewed about her last menstrual bleed (LMP), lenght of the menstrual cycle, and oral contraceptive use, both before surgery and at the time of the first chemotherapy cycle. Information gathered from both interviews were reported on the medical chart and on the on-study record.

Three-hundred and seventy-two patients were in premenopausal status at the time of surgery and complete information about LMP were available in 248 (67%) of them. Patients in whom reliable LMP data could not be retrieved, and patients with history of oral contraceptive use were excluded from further analysis (125 patients, 33%). All patients underwent only one surgical procedure to which we refer hereafter for the evaluation of the menstrual cycle phase at the time of surgery.

Data analysis

Disease-free and overall survival were calculated from the day of surgery to the day of first recurrence or death, respectively, updating follow-up data every 3–6 months. Survival curves were calculated according to the Kaplan–Meier method, and the differences between the curves were analyzed by the log-rank p test.

Cox proportional hazards modeling was used for univariate and multivariate life-table analysis and to estimate the relative risk of recurrence and death associated with the timing of surgery while simultaneously adjusting for the effects of lymph-node status, tumor size, and hormone receptor status. Proportionality of the hazards within subdivisions of each factor was checked by stratifying for each factor in turn, plotting the log minus log of the estimated survival function, and checking both that the resulting curves were roughly parallel for the various strata and that the p values for the other variables did not substantially change from the overall model. All the factors proved to fit the model satisfactorily. The adjusted 5-year survival estimates were obtained by running the Cox model separately for each of the three day intervals between LMP and surgery. A variable representing whether the patient was operated on in that interval or not, along with the other significant factors (tumor size, number of nodes, and receptor status), were entered into the model on each occasion, and an estimated survival function was derived for the interval in question. The 5-year percentages were then calculated from these functions. Confidence intervals (CIs) of 95% and mean standard error (SEM) were given when appropriate.

Table 1. Patient characteristics

Characteristic	All ($n = 248$)	F* ($n = 126$)	L** ($n = 122$)	*P*
Tumor size				
≤ 1 cm	13	8	5	
1.1–2 cm	122	71	51	0.077
> 2 cm	113	47	66	
Lymph nodes				
0	93	50	43	
1–3	81	40	41	NS
≥ 4	74	36	38	
Hormone receptors				
Positive	127	62	65	NS
Negative	121	64	57	
Type of surgery				
Mastectomy	147	66	81	0.03
QUART***	101	60	41	

* Women operated upon during the follicular phase of the menstrual cycle (days 0–14).
** Women operated upon during the luteal phase of the menstrual cycle (days 15–32).
** Quadrantectomy followed by complementary radiotherapy.

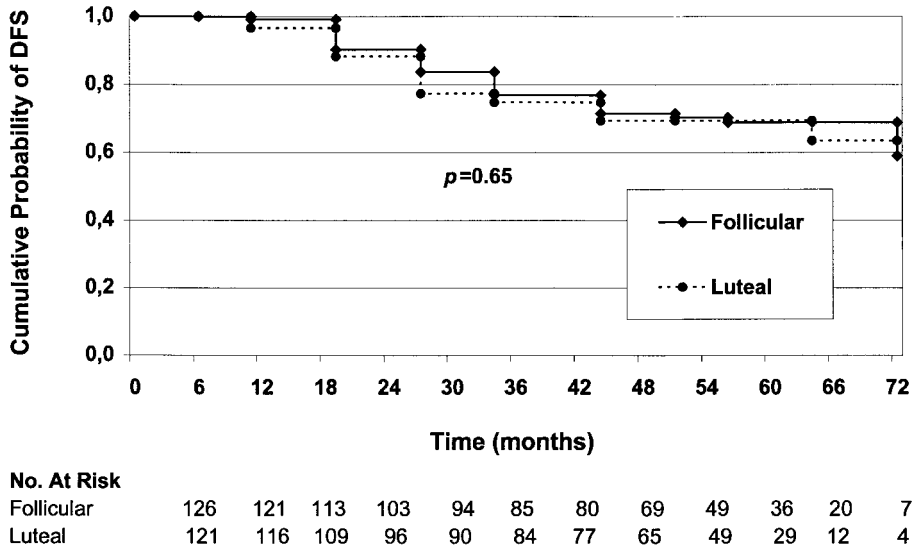

Figure 1. Disease-free survival (DFS) according to the menstrual phase (follicular, days 0–14; luteal, days 15–32) at the time of surgery. Log-rank *p* value for the comparison between the curves = 0.65.

Results

Two hundred forty eight premenopausal patients (67% of 372 premenopausal patients in the database) were fully evaluable with regard to the menstrual cycle phase at the time of surgery. By setting the 14th day after onset of menses as the putative day of ovulation, we divided the menstrual cycle in a follicular (days 0–14) and a luteal (days 15–32) phase, respectively. According to the above reported menstrual cycle division, 126 (51%) out of the 248 evaluable premenopausal patients underwent surgery during the follicular phase and 122 (49%) during the luteal phase. Patient characteristics were well balanced between the

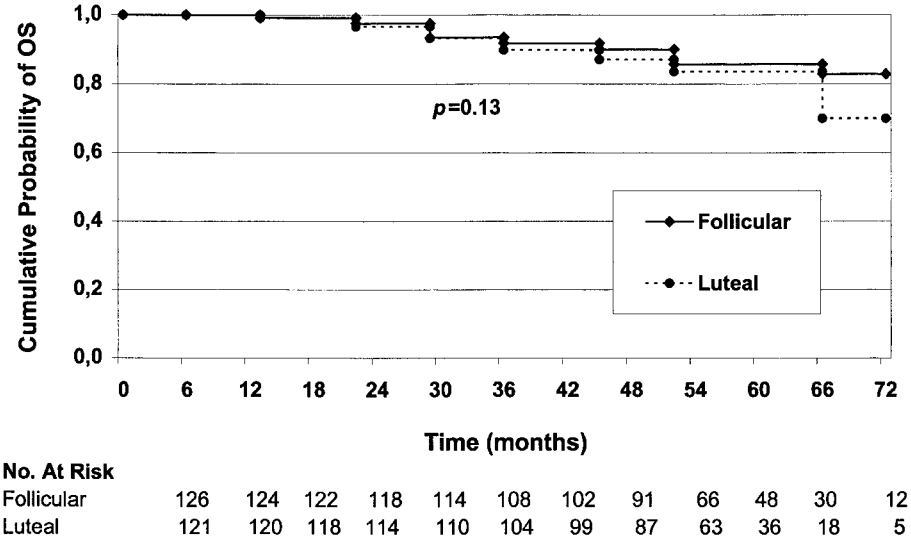

Figure 2. Overall survival (OS) according to the menstrual phase (follicular, days 0–14; luteal, days 15–32) at the time of surgery. Log-rank *p* value for the comparison between the curves = 0.13

Table 2. Univariate and multivariate analysis of prognostic factors

Prognostic factor	Disease-free survival		Overall survival	
	Univariate	Multivariate	Univariate	Multivariate
Menstrual phase	0.66	0.59	0.13	0.44
Lymph-node status	<0.00001	<0.00001	0.003	0.006
Tumor size	0.0001	0.003	0.01	0.07
Hormone receptor status	0.03	0.07	0.01	0.02

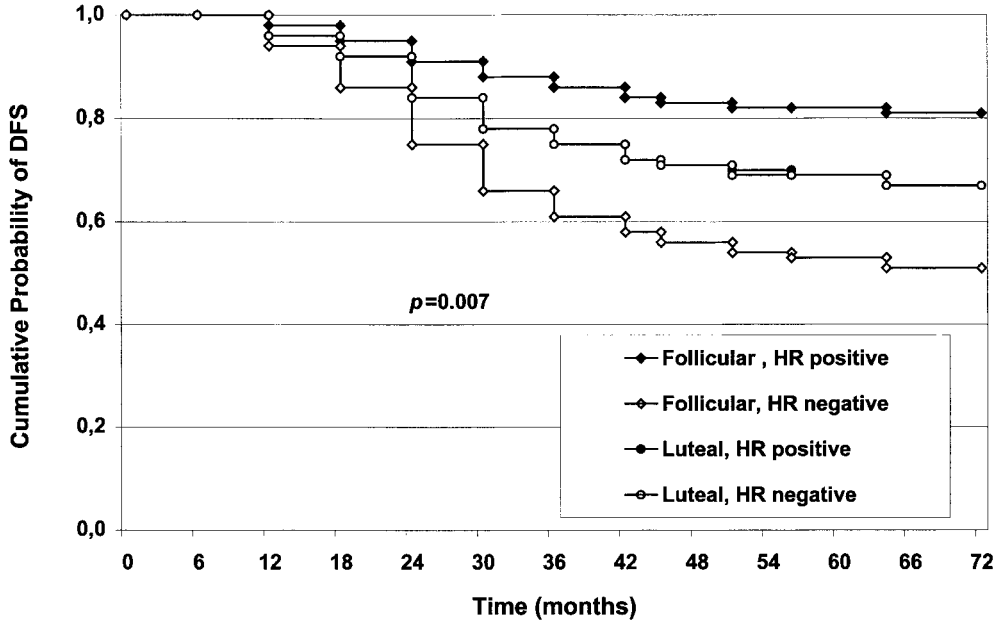

Figure 3. Disease-free survival (DFS) according to menstrual phase (follicular, days 0–14; luteal, days 15–32) at the time of surgery and hormone receptor status (positive or negative), adjusted for tumor size and lymph-node status. Log-rank *p* value for the comparison between follicular, HR positive and all other subgroups = 0.007.

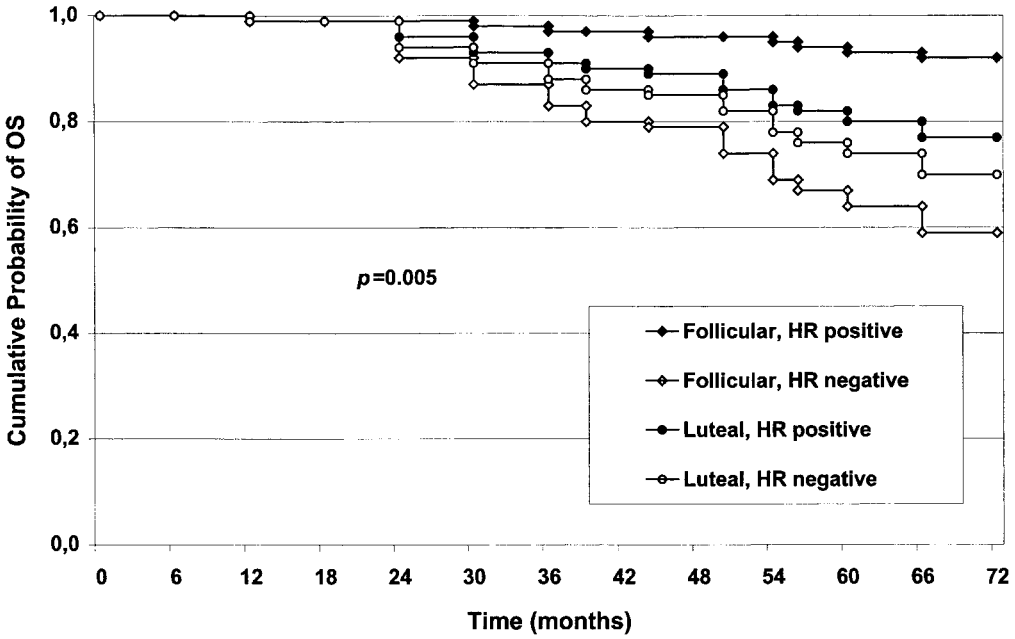

Figure 4. Overall survival (OS) according to menstrual phase (follicular, days 0–14; luteal, days 15–32) at the time of surgery and hormone receptor status (positive or negative), adjusted for tumor size and lymph node status. Log-rank p value for the comparison between follicular, HR positive and all other subgroups = 0.005.

two groups with regard to age (median age 44 years for both groups, range 27–58), lymph-node status, and hormone receptor status; tumor size tended to be greater in the luteal phase group ($p = 0.077$), and a greater proportion of patients operated upon during the luteal phase underwent modified radical mastectomy, as compared to quadrantectomy followed by radiation therapy (Table 1).

Seventy six recurrences and 43 deaths have occurred in the study population, so far. With a median follow-up of 5 years, no statistically significant differences between the follicular and the luteal groups were observed in disease-free (68.9% vs. 68.4%, respectively, $p = 0.65$) or 0S (85.8% vs. 73.9%, respectively, $p = 0.13$) (Figures 1 and 2).

Multivariate analysis indicated that the hazard rate of breast cancer recurrence and death after tumor excision during the follicular phase were 1.60 (95% Cl, 0.87–2.94) and 1.11(95% Cl, 0.70–1.73), respectively. Univariate and multivariate analysis also confirmed the prognostic role of lymph-node status, tumor size, and hormone receptor expression, but not that of the timing of surgery within the menstrual cycle, with respect to disease-free and overall survival (Table 2).

However, when combined with hormone receptor status, the phase of the menstrual cycle at the time of surgery helped to better define the prognosis of primary breast cancer patients. Indeed, even when adjusted for other prognostic factors (i.e. tumor size and lymph-node status), patients with positive hormone receptors undergoing surgery during the follicular phase of their menstrual cycle had a significantly better prognosis in terms of both disease-free and overall survival ($p = 0.007$ and $p = 0.005$, respectively), as compared to the other subgroups of patients (follicular, hormone receptor negative; luteal, hormone receptor positive; luteal, hormone receptor negative) (Figures 3 and 4).

The data were examined further to see whether our interval selection was appropriate. As shown in Figure 5, using the day of surgery within the menstrual cycle as a continuous variable, while simultaneously adjusting for tumor size, lymph-node status, and hormone receptor status, the SEM for different three-day intervals, all completely overlapped the 5-year disease-free and overall survival. χ^2 analysis across multiple bins failed to show any statistically significant difference among the three-day intervals considered (data not shown).

Moreover, we also analyzed our data using different menstrual cycle divisions (0–6, 21–36 vs. 7–20; 0–2, 13–32 vs. 3–12; 0–6 vs. 7–32; 0–6, 15–32 vs. 7–14) that had been demonstrated to impact on disease-free and overall survival in published series

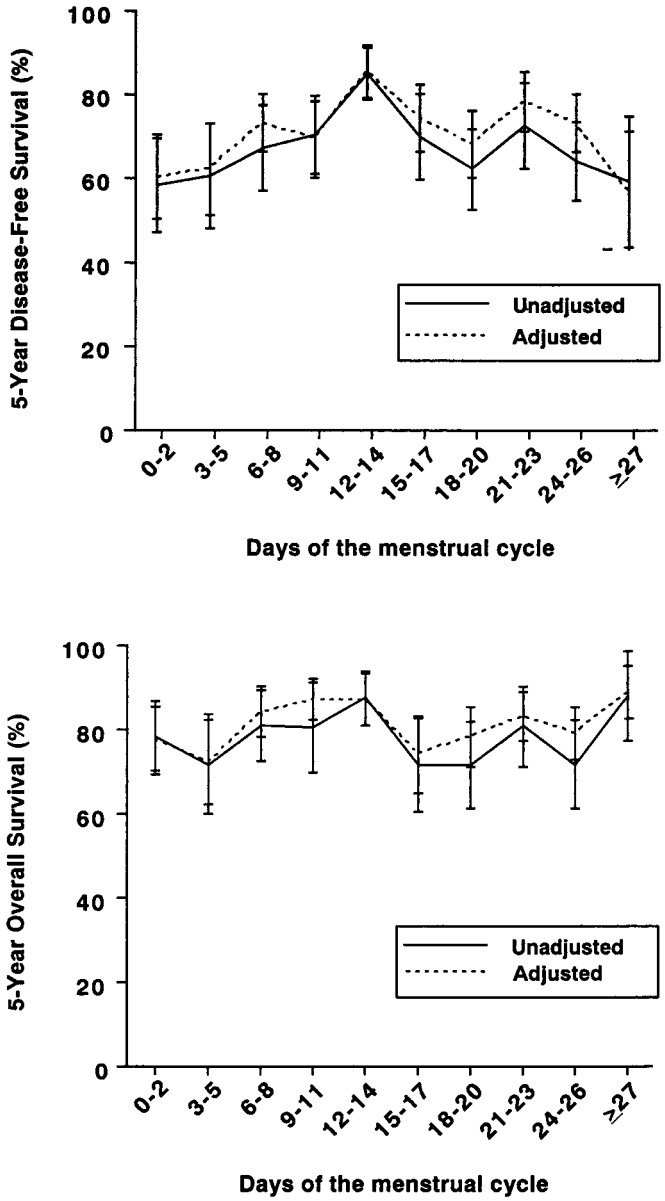

Figure 5. Five-year disease-free (top panel) and overall survival (bottom panel) rates by interval between LMP and operation, adjusted (broken line) or not (continuous line) for tumor size, lymph-node status and hormone receptor status. Vertical bars = SEM.

from other groups [5, 9–14]. In our study population, however, none of these intervals proved to be of statistically significant prognostic value (data not shown).

Discussion

In the present study, we found no evidence to support the hypothesis that timing of surgery in relation to LMP has an influence on outcome of breast cancer patients receiving anthracycline-containing adjuvant chemotherapy.

After the first report of Hrushesky and colleagues [5], many other investigators have surveyed their research databases or medical records to locate dates of LMP and perform survival analysis of their case series. Results from these retrospective studies has produced conflicting results and considerable controversy [15–18], with one additional group finding marginally

significant survival differences [13] and many others not confirming a prognostic effect for tumor excision during perimenstrual versus mid-cycle intervals [14, 18–24].

By setting the 14th day after the onset of menses as the putative day of ovulation, several authors identified a follicular (days 0–14) phase, characterized by unopposed estrogens, and a luteal phase (days 15–32), characterized by elevated estrogen levels accompanied by a rapid rise in progesteron [1, 6]. The studies of Rageth et al. and Sigurdsson et al., each involving more than 200 patients, failed to demonstrate a prognostic role for the menstrual cycle phase at the time of surgery [20, 22]. Conversely, both Senie et al. and Veronesi et al. observed an advantage in disease-free, which was statistically significant only for node positive patients ($p = 0.022$ and $p < 0.03$, respectively), in women undergoing surgery during the luteal phase [14, 25]. In another report, Spratt et al. found a 7-year overall survival of 64% among 30 patients treated during the follicular phase versus 86% among 10 women undergoing surgery during the luteal phase [13]. Saad et al. [26] observed a greater disease-free in patients treated later in the menstrual cycle, especially those with positive axillary nodes.

Badwe et al. [10] created a third division of the menstrual cycle based on mean estrogen and progesterone fluctuations and demonstrated that metastatic spread of disease occurred significantly more frequently among the 249 patients who had surgery during the interval of unopposed estrogens (days 3–12) than among those who had surgery at other times in the cycle when estrogen and progesterone were at similar levels ($p < 0.001$). As in other studies, survival differences were restricted to patients with positive lymph nodes.

In most of these studies the researchers have assigned the date of surgery to the follicular or luteal phases with reference to the date of the first day of the LMP. However, this method has the disadvantage of systematically misclassifying patients whose interval from the last bleed gets longer. The degree of misclassification depends on the lenght of each woman's cycle, because cycle lenght is determined mainly by the lenght of the follicular phase. To overcome this systematic misclassification, Harlap et al. [27] devised an improved method for assigning dates to particular day of the menstrual cycle. Using this method, they showed that, for women who were diagnosed with breast carcinoma in the late 1970s and early 1980s, menstrual timing of surgery did strongly influence subsequent survival, with a significant reduction of the risk of death for patients operated upon in the perioviulatory period. Interestingly, this difference was no longer observed in women undergoing surgery after 1984. Whether or not this change in the prognostic value of timing of surgery within the menstrual cycle is related to the changes in surgical and/or medical management of primary breast cancer in the recent years is not clear.

In addition to a lack of uniformity in divisions of the menstrual cycle, prognostic studies of menstrual timing of surgery have been complicated by a variability in the sources of study populations, in the methods of assessment of the LMP, in the use of post-surgical treatments (e.g. adjuvant therapy), and in the methods of statistical analysis [28]. Compared to other published studies, our study patients were homogeneously treated with the same anthracycline-containing regimen and were accrued over a limited period of time (1991–1994), thereby limiting confounding factors related to the changes in disease management. In our series, neither the follicular versus luteal nor any of the other reported menstrual cycle divisions proved to be of prognostic significance, nor there was significant association between post-operative disease-free and overall survival and the time of surgery, when analyzed using the day of the menstrual cycle as a continuous variable. However, combining the menstrual cycle phase at the time of surgery with hormone receptor status proved to be useful in patients' prognostic assessment, with women operated upon in the follicular phase and with positive hormone receptors having a significantly better outcome. The data on proliferation of breast carcinoma cells during menstrual phases recently reported by Ménard and colleagues [29] might offer an interesting explanation for these findings. In the subgroup of 129 hormone receptor positive cases, the frequency of tumors with high number of mitosis removed during the follicular phase was indeed significantly lower ($p = 0.05$) than for tumors removed during the luteal phase.

In conclusion, the prognostic effect of the menstrual phase at the time of surgery for primary breast cancer remains a controversial issue. A better understanding of the biological changes occurring during different phases of the menstrual cycle, as well as well-designed large prospective clinical trials will be required to definitively answer these questions.

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Address for offprints and correspondence: Michele Milella, Division of Medical Oncology I, Regina Elena Cancer Institute, Viale Regina Elena 291, 00161 Rome, Italy; *Tel:* 39-06-49852201; *Fax:* 39-06-4462655