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BREAST CANCER AND TIMING OF SURGERY DURING MENSTRUAL CYCLE. A 5-YEAR ANALYSIS OF 385 PRE-MENOPAUSAL WOMEN

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It has been proposed that the timing of breast-cancer surgery in relation to menstrual phase has a prognostic impact on outcome. We carefully evaluated a combined 2-center series of 385 pre-menopausal women operated on for stage-I and stage-II breast cancer with a median follow-up of 5 years for a possible impact on outcome of the date of their last menstrual period (LMP) before surgery. The distribution of risk factors of the study cohort as well as prognostic indicators corresponded to previously published results. Nodal status, grading, and (in part) hormone-receptor status differentiate well between patient subgroups with high and low risk of relapse and death after breast-cancer surgery. In neither univariate nor multivariate analysis was any impact of the so-called "unopposed" estrogen secretion detected. We did not observe any effect of LMP on long-term survival in any of several prognostic subgroups, in particular in hormone-receptor-positive patients. From our results and from the literature, we conclude that LMP does not provide any prognostic information for outcome after breast-cancer surgery and therefore the proposed modification of scheduling of breast-cancer operations is not justified.

Adjuvant chemotherapy after breast-cancer surgery has been shown to increase long-term survival, particularly in pre-menopausal women (EBCTCG, 1992). However, breast cancer is still among the most common causes of death in women of this age group, with a mortality of approximately 50% 10 years after surgery.

Some years ago, it was suggested that the timing of surgery in relation to phase of menstrual cycle might affect the long-term survival of patients with operable breast cancer (Hrushesky *et al.*, 1989). This preliminary report was based on the observations from experiments with mice (Ratajczak *et al.*, 1988) and included 41 patients. In 22 women who underwent surgery peri-menstrually, the risk of relapse of and death from breast cancer increased by 300%. Other investigators were not able to replicate these findings, but recently a retrospective analysis of 249 pre-menopausal women (Badwe *et al.*, 1991) confirmed these suggestions. It was concluded that the date of surgery after LMP (last menstrual period) is probably the most important prognostic factor in pre-menopausal breast cancer, even surpassing axillary lymph-node status in its prognostic power. Therefore, observance of the right timing of surgery following the principles of avoiding the pre-ovulatory phase with its "unopposed estrogen secretion" would be mandatory in the future. These findings have led to remarkable confusion among breast-cancer patients and surgeons. Some controversial short reports have been published, some of them including small numbers of patients and/or short follow-up period (Low *et al.*, 1991; Goldhirsch *et al.*, 1991; Powles *et al.*, 1991; Ville *et al.*, 1991; Senic *et al.*, 1991).

The aim of our study was to evaluate a large number of pre-menopausal breast-cancer patients to investigate the validity of these suggestions. We therefore pooled the data from all pre-menopausal women who were operated on for breast cancer in the 2 major breast cancer treatment and research units of Vienna. To ensure comparable conditions, we tried to follow the methodological approach of Badwe *et al.* (1991) as exactly as possible, particularly with respect to patient selection, data presentation and statistical methods.

Because a possible explanation for an effect of menstrual phase on outcome after breast-cancer surgery might be found in different endocrine patterns during the menstrual cycle, we performed several subgroup analyses in order to compare the outcome of different LMP risk groups within several well-defined subgroups as node-positive and node-negative patients or regarding hormone receptor status of the primary tumor.

PATIENTS AND METHODS

Patients

All pre-menopausal patients with operable breast tumors who had received primary treatment either at the First Surgical Department or the First Gynecological Department of the University of Vienna between 1977 and 1989 were identified from a computerized database. Data collection included primary treatment, well-known prognostic factors, adjuvant therapy, date of recurrence or death, last follow-up date and status and date of LMP at the time of the primary surgical treatment. We tried to collect information about period irregularity and intercycle time from the hospital records. After exclusion of patients with tumors larger than 6 cm in diameter, concomitant distant metastases, concomitant or previous malignant diseases and inflammatory or bilateral breast cancer, 687 eligible patients remained for the study population (445 from the Surgical Department, 242 from Gynecology). Of these, 302 had to be excluded from the analysis, 180 of them because there were no adequate data for LMP, 101 because they had irregular periods (amenorrhea for more than 90 days) or were taking oral contraceptives, and 21 for miscellaneous reasons including pregnancy (n = 8), lactation, and hormone replacement therapy. Thus, 385 patients with breast cancer stages I and II (T1–3, N0–1, M0), complying with the selection criteria and having adequate data for LMP, constitute the study population.

In accordance with the published data, our patients were divided into 2 groups: group A, comprising 254 patients whose LMP was 0 to 2 or 13 to 32 days before surgery (comparable estrogen and progesterone levels, considered as the low-risk group), and group B, consisting of 131 patients whose LMP was 3 to 12 days before surgery (unopposed circulating estrogen, considered as the high-risk group).

Therapy and follow-up

Surgical treatment consisted of either conservative breast surgery with axillary dissection (n = 126) or modified radical mastectomy with axillary dissection (n = 259).

Subsequently, 242 patients received adjuvant chemotherapy; 188 of these were included in protocols evaluating different adjuvant treatment regimens, most of which comprised cyclophosphamide, methotrexate and 5-fluorouracil. Some of the

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TABLE I – PATIENT CHARACTERISTICS AND OBSERVED EVENTS AND THEIR DISTRIBUTION BETWEEN LMP SUBGROUPS (N = 385)

	n (%) All patients	LMP low risk (0–2, 13–32) (n = 254)	LMP high risk (3–13) (n = 131)	p^*
Surgical treatment:				
conservative surgery	126 (32.7)	86 (33.9)	40 (30.5)	0.8
modified radical mastectomy	259 (67.3)	168 (66.1)	91 (69.5)	
Grading:				
Grades I and II	177 (46.0)	120 (56.1)	57 (53.8)	0.7
Grade III	143 (37.1)	94 (43.9)	49 (46.2)	
Other histology	65 (16.9)			
Tumor Size:				
T1	179 (46.5)	122 (48.0)	57 (43.5)	0.5
T2	189 (49.1)	123 (48.4)	66 (50.4)	
T3	17 (4.4)	9 (3.5)	8 (6.1)	
Number of affected nodes:	179 (46.5)	119 (46.9)	60 (45.8)	0.8
0	106 (27.6)	71 (28.0)	35 (26.7)	
1 to 3	72 (18.7)	47 (18.5)	25 (19.1)	
4 to 10	14 (3.6)	9 (3.5)	5 (3.8)	
More than 10				
Number positive, number not recorded	14 (3.6)	8 (3.1)	6 (4.6)	
Estrogen receptor:				
Less than 10 fmol/mg	150 (39.0)	98 (41.7)	52 (47.7)	0.3
10 fmol/mg or more	194 (50.4)	137 (58.3)	57 (52.3)	
Not determined	41 (10.6)			
Progesterone receptor:				
less than 10 fmol/mg	152 (39.5)	107 (45.9)	45 (41.3)	0.4
10 fmol/mg or more				
Not determined	190 (49.4)	126 (54.1)	64 (58.7)	
	43 (11.1)			
Age:				
Less than 40 years				
40 years or more	120 (31.2)	74 (29.1)	46 (35.1)	0.2
	265 (68.8)	180 (70.9)	85 (58.7)	
Deaths:	69 (17.9)	47 (18.5)	22 (16.8)	0.7
Recurrences:	98 (25.5)	63 (24.8)	35 (26.9)	0.7
Loco-regional recurrence	32 (8.3)	17 (6.7)	15 (11.7)	0.1 0.5
Distant recurrence only	66 (17.1)	46 (18.1)	20 (15.3)	
Loco-regional and distant recurrence	3 (0.8)	2	1	

*Probability (Chi-square-test).

TABLE II – CO-VARIATES FOR UNIVARIATE AND MULTIVARIATE ANALYSES (N = 385*)

		n (%)
Surgical treatment (OP)	Conservative	126 (32.7)
	Mastectomy	259 (67.3)
Estrogen receptor (ER, n = 344)	Negative	150 (43.6)
	Positive	194 (56.4)
Progesterone receptor (PR, n = 342)	Negative	152 (44.4)
	Positive	190 (55.6)
Grading (G, n = 320)	High grade (I and II)	177 (55.3)
	Low grade (III)	143 (44.7)
Tumor size (T)	Less than 2 cm	179 (46.5)
	2 cm or more	206 (53.5)
Nodal status (N)	Negative	179 (46.5)
	Positive	206 (53.5)
Age	Less than 40 years	120 (31.2)
	40 years or more	265 (68.8)
Adjuvant chemotherapy (Th)	No	143 (37.1)
	Chemotherapy	242 (62.9)
Operation: days after last menstrual period (LMP)	Low risk (0–2, 13–32)	254 (66.0)
	High risk (3–12)	131 (34.0)

*The number of patients is lower for grading and hormone receptors, as indicated. Multivariate analysis (Table VI) includes the 302 patients for whom all co-variates are known.

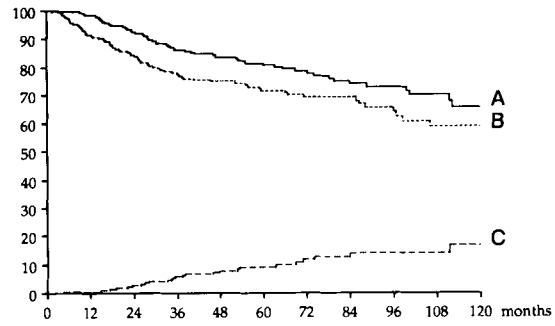

FIGURE 1 – Overall survival, relapse-free-survival and loco-regional recurrence for all 385 patients. A: overall survival; B: relapse-free-survival; C: loco-regional recurrence.

above protocols have already been published (Jakesz *et al.*, 1991). Out of the breast conservation group, 94 patients were post-operatively subjected to standard radiation therapy.

All patients were regularly followed at least every 3 months for the first 3 years and at 6-monthly intervals thereafter. Routine evaluation of patients included clinical examination and laboratory analyses, mammography every 6 months or more frequently if indicated, together with chest X-rays, liver ultrasound and bone scanning whenever clinically indicated (Gnant *et al.*, 1991). Since missing information from a few patients was retrieved through the Central Population Registry of Austria, for this analysis no patient was lost to follow-up.

Histological examination and laboratory assays

Tumor size was defined from the pathologic size immediately after surgery. Histological grade was determined by the method of Bloom and Richardson (1957). Estrogen receptor (ER) and progesterone-receptor (PR) content were assayed by the dextran-coated charcoal method and Scatchard analysis as described previously (Jakesz *et al.*, 1985). A level of at least 10 fmol/mg cytosol protein was considered as receptor-positive.

Statistical analysis

Data were stored in an IBM 3090 computer of the Vienna Medical School using SAS software (SAS Institute, Cary, NC) for data entry, management and analysis. Statistical analyses of survival were based on appropriate programs of BMDP (BMDP Statistical Software, Los Angeles, CA).

Univariate description of continuous factors was performed by estimates of the mean and standard deviations and upper and lower quartiles ($\chi_{0.25}$, $\chi_{0.75}$). Median and quartiles of follow-up time were derived from a Kaplan-Meier analysis with the meaning of the survival status indicator reversed.

Spearman rank-correlation coefficients (r_s) and corresponding tests were used to analyze monotonic associations between the prognostic factors considered. All prognostic factors considered in the analyses were dichotomized using suitable cut-offs to simplify the presentation of results and to more easily judge goodness-of-fit in the modelling process.

Survival was expressed as time from the date of primary treatment of breast cancer to the occurrence of an event and was analyzed in 3 ways: as overall survival (OS), as relapse-free

TABLE III - SPEARMAN RANK-CORRELATION COEFFICIENTS OF CO-VARIATES[1,2] (N = 385)

	OP	ER	PR	G	T	N	Age	Th	LMP
OP	—	NS[3]	NS	NS	−0.27***	−0.14**	NS	NS	NS
ER		—	0.48***	−0.16**	0.1	0.17**	NS	NS	NS
PR			—	−0.14*	NS	NS	0.15**	NS	NS
G				—	NS	NS	−0.11*	0.13	NS
T					—	0.24***	−0.11*	0.16*	NS
N						—	NS	0.21***	NS
Age							—	NS	NS
Th								—	NS
LMP									—

[1]Significance levels achieved: α = 0.05 (*), 0.01 (**), 0.001 (***).–[2]Co-variates are defined in Table II.–[3]NS, not significant.

TABLE IV - UNIVARIATE COMPARISONS OF OS, RFS AND LRFS FOR UPPER AND LOWER LEVELS OF ALL PROGNOSTIC FACTORS

	n	OS			RFS			LRFS		
		group 1[1]	group 2	p[2]	group 1	group 2	p	group 1	group 2	p
OP	385	82.9	76.8	0.4	68.8	80.5	0.3	91.6	88.7	0.2
ER	344	76.8	85.1	0.2	69.2	72.8	0.9	89.6	91.9	0.8
PR	342	74.9	87.4	0.007	64.6	80.0	0.06	89.1	92.3	0.8
G	320	84.5	75.0	0.02	74.2	60.0	0.08	91.3	88.4	0.6
T	385	89.2	74.2	0.006	79.7	60.6	0.004	94.3	88.9	0.2
N	385	90.5	75.2	0.0004	82.9	62.1	<0.00001	92.7	89.8	0.07
Age	385	78.5	82.6	0.2	66.6	73.4	0.2	86.4	93.0	0.2
Th	385	80.0	86.5	0.2	66.0	68.4	0.4	87.4	91.9	0.7
LMP	385	80.4	83.0	0.6	71.6	70.4	0.7	93.9	85.2	0.2

[1]Estimated survival (OS, RFS, LRFS) probabilities 5 years after surgery, by group. Groups defined as in Table II.–[2]Mantel's log-rank test for censored survival data.

survival (RFS), and as loco-regional relapse-free survival (LRFS) or loco-regional recurrence (LR), respectively. RFS was defined as the interval between at the date of operation and the first recurrence of breast cancer. Survival curves for all analyses were calculated according to the method of Kaplan and Meier. Differences between curves were assessed with Mantel's log rank test for censored survival data.

Multivariate analysis by Cox's proportional hazards model served to quantify and confirm the role of prognostic factors after simultaneous adjustment for all other factors considered. In a step-wise fashion, all prognostic factors were eliminated from the model for which no independent effect on survival could be confirmed ($p > 0.15$). Candidates for the final factors in the model were all co-variates listed in Table II.

In all these modelling processes goodness-of-fit was judged by exploratory analyses of possible interactions and time-dependent effects of prognostic factors. Before performing the Cox model, we used a time-dependent co-variate in order to test the proportionality assumption according to the method of Kalbfleisch and Prentice.

In all Cox analyses reported, 2-sided p-values are accompanied by estimates of the relative risk of death (RR) including 95% confidence interval (95% CI), comparing the unfavorable to the more favorable level of each factor.

RESULTS

Overall survival of the patients for whom data about LMP was not known (n = 180) did not differ from that of the study population ($p = 0.6$), confirming the randomness of availability of these data. For clinical characteristics and outcome, no difference was observed between the 2 contributing study centers ($p = 0.9$). Patient characteristics and observed events did not differ between the 2 LMP groups (Table I).

The median follow-up time was 60 months ($\chi_{0.25}$, = 28.1 months, $\chi_{0.75}$ = 84.1 months); as of their last recorded follow-up evaluation, 324 patients (84.2%) were alive and 287 (74.5%) had had no recurrence. Patient characteristics, treatments and observed events are summarized in Table I, and dichotomized data on which analyses are based in Table II.

Correlation of co-variates

The correlation of co-variates is given in Table III.

Operative technique correlated with both tumor size (T) and nodal status (N), ER correlated well with PR and N, grading (G) correlated with both hormone receptors. Age correlated with PR, G and T, and adjuvant therapy with T and N. LMP did not correlate with other co-variates, nor could we find significant correlations between all other combinations of co-variates.

Univariate analysis

Overall survival was 98.4, 92.6, 86.0, 81.3 and 65.4% at 1, 2, 3, 5 and 10 years, respectively. The corresponding figures for RFS are 91.1, 84.3, 77.3, 71.2 and 58.4% and 99.5, 97.3, 94.4, 90.9 and 83.4 for LRFS (Fig. 1).

Univariate analysis performed with all the co-variates listed in Table II revealed that N, P, T and G were able to distinguish between patient groups at high and low risk for death from and relapse of the disease (Table IV). Only N showed some predictive value with respect to loco-regional metastases.

Neither operative technique, estrogen-receptor status, progesterone-receptor status, age group, adjuvant therapy nor LMP bore any prognostic significance in this univariate analysis. As shown in Figure 2, the survival curves for the 2 LMP risk groups are almost identical; however there is a small trend towards more loco-regional recurrences in the high-risk group, which does not reach statistical significance.

Multivariate analysis

Since there are strong correlations between some of the variables (Table III), a Cox model was performed in order to investigate the individual prognostic strength of each co-variate. Results are shown in Table V. Nodal status was seen to

be the most powerful prognostic parameter, with markedly poor outcome with respect to OS, RFS and LRFS. Grading is also an important factor for prognosis, and borderline effects of hormone receptors and age group are shown. Tumor size does not bear any prognostic significance in itself; its power in the univariate model derives from its strong correlation with nodal status. Adjuvant therapy was able to increase RFS, but not OS. No effect at all could be demonstrated for the 2 different LMP risk groups.

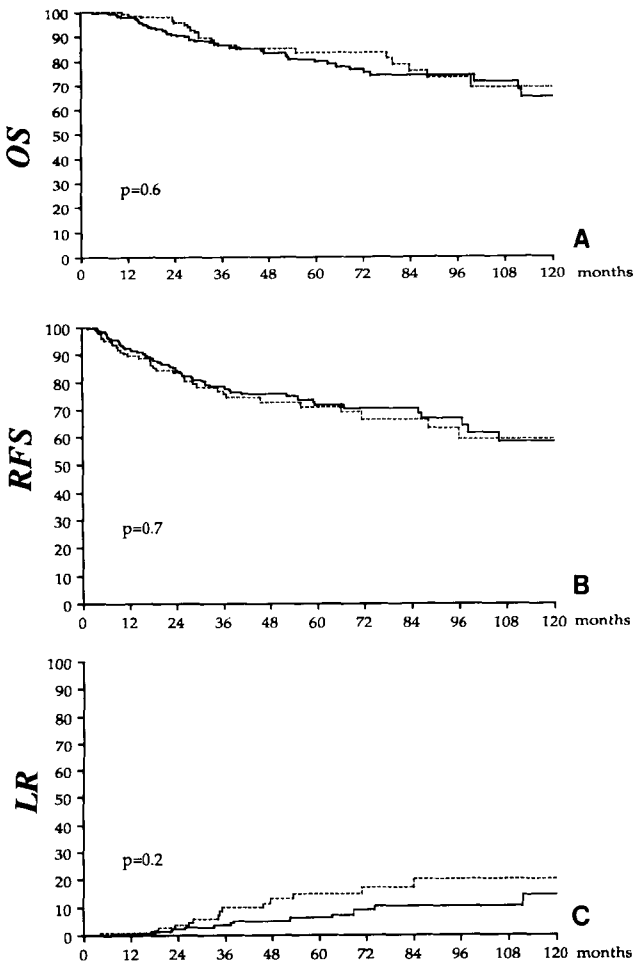

FIGURE 2 – OS, RFS, and LR for different LMP risk groups. Solid line: LMP low-risk group (days 0–2 and 13–32, n = 254); dotted line: LMP high-risk group (days 3–12, n = 131). p = probability of Mantel's test.

We next performed several subgroup analyses according to different risk factor levels of well-known or supposed risk factors. As shown in Table VI, no significance could in general be found for the 2 LMP risk groups.

DISCUSSION

We have analyzed 385 pre-menopausal women operated on for stage-I and -II breast cancer. The risk factors we found correspond with many previously published results. Nodal status was the best parameter discriminating between patients at high and low risk for relapse and death; this is in accordance with many other study groups and meta-analyses (EBCTCG, 1992). The individual prognostic strength of tumor size is still under debate (Sigurdsson *et al.*, 1990). We have, like several other study groups, shown that this parameter has a remarkable impact on outcome in univariate analysis, but multivariate modelling reveals that its impact is related to its strong correlation with nodal status and that tumor size in itself is not an independent marker for outcome. Grading is a good prognostic parameter even in the Cox model. We and others have previously shown that hormone receptor status is a risk factor for relapse-free survival (Reiner *et al.*, 1990).

For both overall and relapse-free-survival, we did not observe any impact of LMP on outcome. This is in clear contrast with the findings of the Guy's Hospital group (Badwe *et al.*, 1991). What are the possible explanations for the marked difference between the results of Badwe *et al.* and our own? The patient cohorts are quite comparable: out of a total of 687 patients treated within the study period, 385 (56%) could be included for analysis in our series, as compared to 249 out of 560 (44%) in the series of Badwe *et al.* The age distribution, tumor size, pattern of grading, number of affected lymph nodes, and both estrogen and progesterone receptor status were quite comparable in the 2 study groups. The only differences in patient characteristics were the higher rate of breast-conservation surgery in our group (33% as compared to 22%) and the fact that more patients of our cohort were included in adjuvant treatment protocols. Both differences can be explained by the later recruitment period of our investigation, when modern treatment strategies were better established. The later recruitment period is also responsible for the shorter median follow-up of our cohort (5 years as compared to 9 years), however, a median observation period of 60 months is quite acceptable for prognostic factor studies. Furthermore, an approximate 25% survival and relapse-free difference between the 2 LMP risk groups at 5 years can be estimated from Badwe's figures, which we were quite unable to reproduce. Moreover, prognostic effects of potential risk factors which are valid at 10 years are usually present after 5 years of follow-up.

In order to investigate the biometric validity of the "negative" results of our study, we have calculated the possibility of a

TABLE V – MULTIVARIATE ANALYSIS (COX PROPORTIONAL HAZARDS REGRESSION) OF PROGNOSTIC CO-VARIATES IN 302 PATIENTS FOLLOWED UP FOR A MEDIAN OF 5 YEARS[1]

Co-variate	OS		RFS		LRFS	
	p	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)
OP	0.7	—	0.3	—	0.8	—
ER	0.02	0.40 (0.27–0.60)	0.8	—	0.3	—
PR	0.9	—	0.07	0.62 (0.47–0.81)	0.9	—
G	0.009	2.77 (1.86–4.12)	0.009	2.10 (1.58–2.79)	0.8	—
T	0.3	—	0.2	—	0.8	—
N	0.0006	4.24 (2.65–6.76)	<0.0001	3.71 (2.66–5.16)	0.009	5.25 (2.45–11.24)
Age	0.06	0.49 (0.34–0.71)	0.2	—	0.08	0.40 (0.24–0.68)
Th	0.2	—	0.03	0.46 (0.33–0.64)	0.3	—
LMP	0.5	—	0.5	—	0.2	—

[1]RR denotes relative risk, 95% CI denotes 95% confidence interval; co-variates and group definition as described in Table II.

TABLE VI – UNIVARIATE 5-YEAR OS ESTIMATES FOR LMP IN DIFFERENT PROGNOSTIC SUBGROUPS (N = 385)

	LMP Low risk (0–2, 13–32) (n = 254)	LMP High risk (3–13) (n = 131)	p^1
Surgical treatment:			
conservative surgery	80.5	87.2	0.2
modified radical mastectomy	81.5	63.5	0.6
Grading:[1]			
I and II	85.3	83.0	0.9
III	70.9	82.3	0.8
Tumor size:			
T1	88.7	90.3	0.4
T2	73.9	80.1	0.2
T3	48.6	50.0	0.7
Nodal status:			
negative	90.7	90.4	0.9
positive	74.4	76.4	0.4
Number of affected nodes[1]:			
1 to 3	87.6	78.3	0.6
4 to 10	58.1	79.7	0.06
more than 10	37.5	20.0	0.6
Estrogen receptor[1]:			
negative	75.8	78.0	0.5
positive	83.3	88.9	0.2
Progesterone receptor[1]:			
negative	75.6	72.9	0.9
positive	84.0	93.7	0.04
Age:			
less than 40 years	78.4	78.7	0.9
40 years or more	81.2	85.6	0.2
Therapy:			
no	77.4	83.3	0.7
adjuvant chemotherapy	83.6	91.9	0.2

[1]Categories include fewer subjects, according to Table II.

type-II error in our study using the method of computer simulation. In short, 1,000 random trials were generated following the survival differences of the alternative hypotheses using the distribution of observation times in our empiric sample. If there were only a 13% survival difference between the 2 LMP risk groups at 5 years (87 *vs.* 74%)—which is only half the difference that was observed by Badwe *et al.* (1991)—we would have detected it with a power of 81% at a significance level (one-sided) of 0.05. Thus, the probability of overlooking a survival difference between the 2 LMP risk groups is virtually minimal. Furthermore, the 95% confidence interval of LMP in the Cox model ranges from 0.52 to 1.45, also clearly indicating that this factor's correlation with outcome is rather accidental.

Several other investigators (Low *et al.*, 1991; Goldhirsch *et al.*, 1991; Powles *et al.*, 1991; Ville *et al.*, 1991; Gelber and Goldhirsch, 1989) were also unable to confirm any effect of LMP on outcome after breast-cancer surgery. In their reports a total of 828 pre-menopausal breast-cancer patients have been investigated, without any impact of timing of surgery within the menstrual cycle. A group from the Memorial Sloan-Kettering Cancer Center in New York, however, presented findings similar to those of Badwe *et al.* (1991)—a higher rate of recurrence following mastectomy during days 7 to 14 of the menstrual cycle in a cohort of 283 patients (Senie *et al.*, 1991). The definite reasons for the clear discrepancy between their results and those of all other study groups remain unclear. Recently, McGuire *et al.* (1992) published a very elegant simulation study in order to assess whether the results of Badwe and of Senie could have been spurious and due to chance alone. When these authors randomly assigned a fictious LMP integer to each of the 675 patients from their tumor bank, they found a "significant" result in 28% of their simulations. Their findings suggest that the prognostic significance of LMP which can be found in the minority of studies performed on this parameter and published to date may actually be spurious.

Thus, treatment of breast cancer will have to rely on well-established and confirmed prognostic parameters such as nodal status and grading to come to treatment decisions for individual patients. However, within recent years, several new parameters have been established and confirmed, *e.g.* parameters derived from DNA flow cytometry (Clark *et al.*, 1989; Beerman *et al.*, 1990; Gnant *et al.*, 1992) or genetic analyses (Slamon *et al.*, 1989; Colm *et al.*, 1991).

A mandatory modification of surgical planning in pre-menopausal breast cancer patients, as proposed by Badwe *et al.*, appears not only premature but also unjustifiable. The attention focused upon their findings by the media has caused uncertainty and anxiety among breast-cancer patients, which, as we have shown, is unnecessary. In our opinion, further investigation of this parameter in a prospective and controlled fashion is unwarranted, since there was no confirmatory indication or trend, either in our analysis or in those of others.

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