Breast Cancer Survival and the Timing of Tumor Removal during the Menstrual Cycle[1]

Shine Chang,[2] Barbara S. Hulka, Donna D. Baird, James N. Ingle, Beth Newman, Mark L. Graham II, Bahjat Qaqish, John H. Donohue, and L. Joseph Melton III

Departments of Epidemiology [S. C., B. S. H., B. N.] and Biostatistics [B. Q.], School of Public Health, and Division of Hematology/Oncology, School of Medicine, [M. L. G.], University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-7400; Department of Epidemiology, Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina [D. D. B.]; and Division of Medical Oncology [J. N. I.] and Departments of Surgery [J. H. D.] and Health Sciences Research [L. J. M.], Mayo Clinic, Rochester, Minnesota 55905

Abstract

In a retrospective cohort study of 262 premenopausal breast cancer patients treated at the Mayo Clinic between 1965 and 1985, we investigated whether survival was associated with the timing of tumor removal during the menstrual cycle. Participants were women ≤50 years old who had not used exogenous hormones, been pregnant, been lactating, or given birth within 6 months of diagnosis. The menstrual cycle day at surgery was used to assign women to group 1 (cycle days 0–7), group 2 (cycle days 8–15), or group 3 (after cycle day 15). Cox proportional hazards analysis adjusting for age at diagnosis, stage, tumor size, grade, and node involvement showed a nonsignificantly worse survival for group 2 than for group 3 [hazard ratio (HR), 1.41; 95% confidence interval (CI), 0.89–2.23]. Stratification revealed that the association between survival and timing of tumor removal during the menstrual cycle was slightly stronger among patients with stage II disease (adjusted HR, 1.56; 95% CI, 0.92–2.63). The association was the same among patients with stage II disease and node involvement (adjusted HR, 1.57; 95% CI, 0.82–3.03). Prospective studies using hormone measurements to define menstrual cycle status more accurately than the reported day of the menstrual cycle could provide further insight about the postulated association.

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[2] To whom requests for reprints should be addressed, at Department of Epidemiology, Box 189, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030-4095. Phone: (713) 745-2729; Fax: (713) 792-0807; E-mail: schang@notes.mdacc.tmc.edu.

Introduction

The conventional prognostic indicators of breast cancer survival include primary tumor size, histopathological type, tumor grade, number of axillary lymph nodes involved, and extent of metastasis. Recently, interest has been generated in the potential prognostic value of the timing of tumor removal during the menstrual cycle. In a study of 44 women conducted in 1989, patients who had surgery between menstrual cycle days 7 and 20 survived longer than patients who had surgery at other times (1). The investigators hypothesized that hormone levels influence NK[3] cell activity, resulting in longer survival for women who had surgery near the time of ovulation. However, NK cell activity decreased in mice after administration of estradiol and was associated with a concomitant, higher frequency of metastasis (2). In women, immunological suppression of NK cells has been associated with rising levels of estrogen during the follicular phase (3) and has been observed in premenopausal breast cancer patients compared with healthy women (4). Several subsequent studies suggested that surgery during the follicular phase, before day 12 or 14, resulted in poorer survival of patients with axillary lymph node involvement (5–9). Senie *et al.* (6) found that women who had surgery between days 7 and 14 had particularly poor survival. However, other researchers using follicular-luteal phase comparison groups were unable to confirm these findings (10–26). Investigations have differed in source populations, inclusion and exclusion criteria, menstrual cycle divisions, outcomes (*i.e.,* death or recurrence), and methods of statistical analysis. Consequently, whether a woman's hormonal environment at the time of tumor removal affects her survival remains unclear.

We investigated the association between overall survival and the timing of tumor removal during the menstrual cycle in a retrospective cohort study of premenopausal breast cancer patients treated from 1965 to 1985 at the Mayo Clinic. This population offered unique advantages for examination of this issue because of the relatively infrequent use of needle biopsy as a diagnostic test, the application of a one-step breast surgical procedure (*i.e.,* radical or modified radical mastectomy) for most patients, and the relatively low use of adjuvant therapy during the study period. Furthermore, the uniform system of medical records at Mayo and its institutional cancer registry facilitated retrieval of data such as menstrual cycle characteristics and vital status at follow-up. Our *a priori* hypothesis was that tumor removal during the mid-to-late follicular phase would result in a shorter overall survival than when surgery is performed in the luteal phase. On the basis of findings reported by others (5, 6), we hypothesized that surgery would have the greatest influence on the survival of those with operable disease (stage II) and axillary lymph node involvement.

[3] The abbreviations used are: NK, natural killer; LMP, last menstrual period; ER, estrogen receptor; HR, hazard ratio; CI, confidence interval.

Materials and Methods

Subject Selection. We identified potential subjects from two computerized databases, the Cancer Registry and the Surgical Index. Among the 1145 patients ≤50 years old seen for breast cancer from 1965 to 1985, 562 women were diagnosed with primary breast cancer, had surgery, and resided in the United States. From this group, women were excluded if they had undergone hysterectomy or bilateral ovary removal or were otherwise postmenopausal (n = 85) or if they were recent (within 6 months) or current users of hormone replacement therapy (n = 17) or oral contraceptives (n = 75). Twenty-one other women were excluded because they were pregnant, lactating, or within 6 months of a live birth. Fourteen women were excluded for having *in situ* breast cancer, Paget's disease of the nipple, inflammatory disease, and cystosarcoma phylloides.

Data Collection. Data were abstracted from each woman's medical records by the same abstractor (S. C.), who used a pilot-tested, precoded form. The medical records documented the outpatient and inpatient care received a the Mayo Clinic's affiliated hospitals (St. Mary's Hospital and Rochester Methodist Hospital); the results of all diagnostic and laboratory test results, including pathological studies; and correspondence regarding the patient's health care (27). The latter included annual vital status follow-up by the Cancer Registry. The data collected were used to characterize the patient's menstrual cycles (including regularity and date of LMP before breast cancer surgery), disease at diagnosis, types and numbers of surgical procedures performed on different days, adjuvant therapy, and survival.

Outcome was defined as survival until death from breast cancer or censorship at the last Mayo contact before the study closing date of December 1, 1992. Survival time was measured in months from the date of tumor removal to either end point. The Cancer Registry conducts vital status surveillance according to the requirements for cancer registries outlined by the American College of Surgeons, including annual vital status follow-up of every cancer patient. Overall, 90% had reported vital status within 3 years of the study closing date; by menstrual cycle groups, completeness of follow-up was 94, 91, and 89% for groups 1, 2, and 3, respectively. Dates of death were recorded from death certificates obtained by the Cancer Registry, and deaths unrelated to breast cancer were censored at death (n = 9). Menstrual cycle day was calculated by subtracting the LMP date before surgery from the date of tumor removal and was used to assign subjects to three groups according to menstrual cycle intervals: days 0–7 (group 1), days 8–15 (group 2), and after day 15 (group 3).

Tumor size, number of axillary lymph nodes involved, and distant metastasis were categorized according to definitions used by the American Joint Committee on Cancer (28). Disease stage at diagnosis was determined by the TNM criteria (Ref. 28; Table 1). Tumors with ER levels ≥10 fmol/mg were considered ER positive; however, ER status was not measured routinely at Mayo until 1977. The women were divided into two groups based on year of surgery to assess whether survival effects were apparent after 1974 when use of adjuvant chemotherapy became more common.

For multivariable analyses, age was treated continuously. Tumor size in centimeters (≤2, 2–5, or >5), stage (I, II, or III-IV), and grade (1–2, 3, or 4) were treated categorically. All other variables were dichotomized [node involvement, number of surgeries (1 *versus* >1), type of surgery (radical mastectomy *versus* other), chemotherapy, menstrual cycle regularity (regular *versus* irregular), ER status, and surgery after 1974].

Statistical Methods. For crude analyses, we compared 10-year survival probabilities and used Kaplan-Meier survival curves and log-rank tests (29). For multivariable analyses, Cox proportional hazards modeling and the likelihood ratio test were used to evaluate survival differences between menstrual cycle groups (29). HRs with 95% CIs and Ps were computed for menstrual cycle groups 1 and 2 compared with group 3, the group hypothesized to have the best survival. We included the prognostic factors age at diagnosis, stage, tumor size, grade, and node involvement as covariates whether or not the particular variable was statistically significant in the model to control for potential confounding. We evaluated for effect modification by number and type of surgeries, chemotherapy, menstrual cycle regularity, and surgery before 1974 by including product terms (menstrual cycle group × variable) in the fully adjusted model. There were too few women with known ER status to evaluate effect modification by this characteristic.

Further proportional hazard analyses were done with stratification by stage and node involvement to assess whether menstrual cycle group was more strongly associated with survival for women with stage II, node-positive disease, as had been reported previously. These subgroup analyses controlled for the same prognostic factors used in analyses of the complete data set.

Results

Among the 350 women who were eligible for the study, 262 (75%) reported LMP dates before surgery. Although only these women could be used in the analysis, they did not differ in overall survival from the 88 otherwise eligible subjects who did not report a LMP date (median survival, 148 and 135 months, respectively; P = 0.85) or in the distributions of other characteristics (data not shown).

Baseline Characteristics. Clinical and pathological characteristics of women reporting LMP dates are presented in Table 1. Mean age at diagnosis was 41 years (range, 25–46 years). Most of the women had surgery on or before menstrual cycle day 32 (n = 244; 93%). There were 35 women (13%) in group 1, 54 (21%) in group 2, and 173 (66%) in group 3. The distribution of women by menstrual cycle day may have been skewed because surgery scheduled randomly would have had a higher probability of taking place during a long cycle in which most of the days would have been after day 15.

Two-hundred twenty-six women (86%) had invasive ductal carcinoma. Eight others had infiltrating lobular carcinoma, and eight had tumors specified only as "adenocarcinoma" or "cancer." Stage could not be assigned for 21 women (8%); they were grouped with stages III and IV, because their median survival (31 months) was similar to that of women with stage III or IV disease (P = 0.23). Ninety-six % of the women had modified radical, simple, or radical mastectomies. There were 52 women (20%) who had surgeries on 2 days and 4 who had surgeries on 3 days (2%). Altogether, 64 women had documented chemotherapy within 65 days of tumor removal.

A larger percentage of women in groups 1 and 2 (compared with group 3) had stage II disease or higher and some lymph node involvement (Table 1). Group 2 had proportionately more women than the other groups, with tumors greater than 2 cm in diameter. Group 1 had a higher proportion of patients with stage III or IV disease. Women in the menstrual cycle groups were fairly evenly distributed with regard to distant metastases, histological grade, ER status, number and

Table 1 Distribution of women by menstrual cycle interval at surgery and selected clinical and pathological characteristics

Characteristics	Menstrual cycle interval at surgery[a]			P^b
	Group 1 (n = 35) n (%)	Group 2 (n = 54) n (%)	Group 3 (n = 173) n (%)	
Stage at diagnosis				0.30
I	4 (11)	5 (9)	39 (23)	
II	21 (60)	38 (70)	96 (55)	
III	8 (23)	5 (9)	17 (10)	
IV	0 (0)	1 (2)	7 (4)	
Not recorded	2 (6)	5 (9)	14 (8)	
Tumor size (cm)				0.12
≤2.0	12 (36)	11 (21)	73 (43)	
>2.0 to 5.0	16 (48)	38 (72)	78 (46)	
>5.0	5 (15)	4 (8)	20 (12)	
Axillary lymph nodes				0.18
0	13 (39)	21 (40)	77 (48)	
1–3	9 (27)	15 (29)	54 (34)	
>3	11 (33)	16 (31)	30 (19)	
Distant metastasis at diagnosis[c]				
No	34 (100)	50 (98)	154 (96)	
Yes	0 (0)	1 (2)	7 (4)	
Histological grade				0.74
1, 2, or 3	10 (29)	17 (31)	60 (35)	
4	25 (71)	37 (69)	113 (65)	
ER status				0.97
Positive	9 (56)	12 (52)	35 (54)	
Negative	7 (44)	11 (48)	30 (46)	
Number of breast surgeries[d]				0.77
1	26 (74)	42 (78)	138 (80)	
>1	9 (26)	12 (22)	35 (20)	
Types of surgical procedures				0.81
Radical mastectomy	8 (23)	13 (24)	40 (23)	
Modified radical or simple	24 (69)	40 (74)	126 (73)	
Biopsy and other	3 (9)	1 (2)	7 (4)	
Report of chemotherapy within 65 days[e]				0.43
No treatment	23 (68)	32 (60)	119 (70)	
Treatment	11 (32)	21 (40)	51 (30)	
Age at diagnosis (years)				0.63
≤40	12 (34)	24 (44)	71 (41)	
>40	23 (66)	30 (56)	102 (59)	
Menstrual cycle regularity				0.49
Regular	25 (71)	44 (81)	139 (80)	
Irregular	6 (17)	4 (7)	22 (13)	
Not reported	4 (11)	6 (11)	12 (7)	
Years of surgery				0.89
>1974	22 (63)	33 (61)	102 (59)	
≤1974	13 (37)	21 (39)	71 (41)	

[a] Numbers may not equal n because of missing data.
[b] Based on standard χ^2 test for contingency tables.
[c] Lack of observations in cells prevented calculation of the standard χ^2 test for contingency tables; therefore, no P is given.
[d] Total number of days on which breast surgery occurred.
[e] Where there was no report of chemotherapy treatment, no treatment was assumed except for patients diagnosed with axillary lymph node involvement after 1974. Chemotherapy treatment was assumed for patients with node involvement diagnosed after 1974.

type of surgical procedures, use of chemotherapy, menstrual cycle regularity, and surgery after 1974 (Table 1).

Influence of Menstrual Cycle on Survival. As shown in Table 2, overall 10-year survival was worse for patients in group 2 (44%) than for those in groups 1 (56%) and 3 (54%). Ten-year survival was somewhat worse for group 2 than for either group 1 or 3 among most patient subgroups regardless of prognostic factor. However, a particularly low survival of group 1 women among those ≤40 years old showed a statistically significant subgroup difference (Table 2). Kaplan-Meier survival curves are shown in Fig. 1 for the three groups. No significant differences in survival were noted. Average survival for groups 1, 2, and 3 were 8.7, 7.9, and 9.4 years, respectively. Unadjusted survival analysis showed a nonsignificantly poorer survival for group 2 than for group 3 (HR, 1.35; 95% CI, 0.90–2.04).

As shown in Table 3, analysis controlling for age, stage, tumor size, grade, and node involvement produced a HR of 1.41 (95% CI, 0.89–2.23) for group 2 relative to group 3. There was no indication of confounding or effect modification by number and type of surgery, chemotherapy, menstrual cycle regularity, and surgery after 1974. After stratification by stage and adjustment by age, there was no survival difference between group 2 and group 3 women with stage I disease (HR, 0.98; 95% CI,

Table 2 Ten-year breast cancer survival probability (%) by menstrual cycle interval at surgery and selected clinical and pathological characteristics

Characteristics	Total n = 262	Menstrual cycle interval of surgery			P
		Group 1 n = 35	Group 2 n = 54	Group 3 n = 173	
10-year survival					0.27[a]
	52	56	44	54	
Stage at diagnosis					0.79[b]
I	83	100	80	82	
II	52	66	43	53	
III, IV, or not recorded	26	15	29	27	
Tumor size (cm)					0.15
≤2.0	70	83	61	70	
>2.0–5.0	46	50	45	45	
>5.0	25	40	0	28	
Axillary lymph node number					0.82
0	67	62	60	70	
1–3	52	78	43	51	
>3	28	45	19	27	
Histological grade					0.91
1, 2, or 3	68	79	68	66	
4	43	47	32	46	
ER status					0.50
Positive	44	63	32	49	
Negative	42	43	45	41	
Number of breast surgeries					0.64
1	47	46	39	50	
>1	72	89	63	71	
Types of surgical procedures					0.88
Radical mastectomy	48	50	38	50	
Modified radical or simple	54	61	45	54	
Reported chemotherapy within 65 days[c]					0.88
Treatment	42	55	31	43	
No treatment	57	60	49	58	
Age at diagnosis (years)					0.01
≤40	47	17	43	53	
>40	56	78	44	54	
Menstrual cycle regularity					0.96
Regular	52	55	45	54	
Irregular	61	67	50	62	
Not reported	40	50	33	42	
Year of surgery					0.80
>1974	47	54	30	50	
≤1974	60	61	61	59	

[a] This P is based on a log-rank test.
[b] This and the remaining Ps are based on a likelihood ratio test performed within Cox proportional hazards modeling, testing the contribution of interaction between grouped menstrual cycle, day of surgery, and prognostic factor.
[c] Where there was no report of chemotherapy treatment, no treatment was assumed except for patients diagnosed with axillary lymph node involvement after 1974. Chemotherapy treatment was assumed for patients with node involvement diagnosed after 1974.

0.12–8.12). Among those with disease stage III or IV disease or unstaged disease, survival adjusted for age, tumor size, grade, and node involvement was not significantly different for group 2 than for group 3 (HR, 1.29; 95% CI, 0.50–3.32). For stage II, however, the relative hazard of death from breast cancer was somewhat higher for group 2 compared with group 3 (HR, 1.56; 95% CI, 0.92–2.63). When women with stage II disease were stratified by node status and the HR was adjusted for age, tumor size, and grade (Table 4), the HR indicated nonsignificantly poorer survival for group 2 relative to group 3 node-positive women (HR, 1.57; 95% CI, 0.82–3.03).

Discussion

Among the total sample of women in our study, there was no significant difference in survival among menstrual cycle groups 1, 2, and 3, although poorer survival was suggested for women with breast surgery on days 8–15 of the menstrual cycle relative to those with surgery after day 15 in crude comparisons and after adjustment for known prognostic factors. After stratifying by stage at diagnosis and adjusting for other known prognostic factors, poor survival for group 2, albeit nonsignificant, appeared to be concentrated among those with stage II disease and particularly among those with stage II, node-positive disease.

Our findings are consistent with the results of some other studies. Several studies found that the association between breast cancer survival and the timing of surgery during the menstrual cycle was stronger for node-positive than for node-negative patients (5–9). Additionally, poorer survival was associated with the timing of surgery during the unopposed estrogen phase of the menstrual cycle, although that phase was defined in different ways: the "estrogenic phase" (9), days 0–14 (6, 8), days 1–14 (30), days 3–12 (5, 10, 31), and days 1–12 (7). Thus, in those studies in which an association has been found, it has been most evident among patients with operable disease

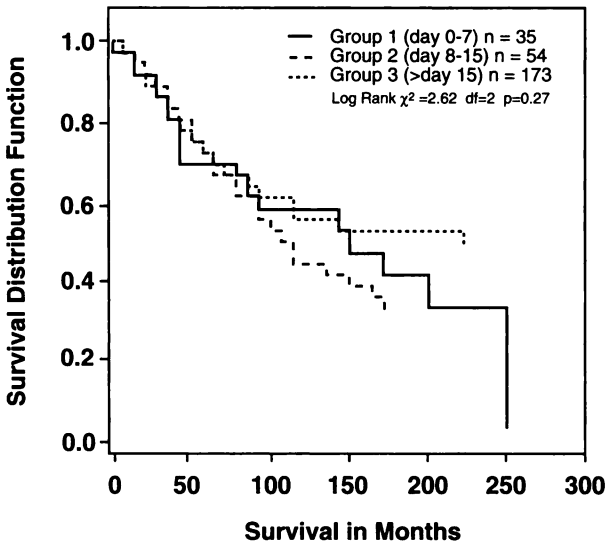

Fig. 1. Breast cancer survival for all patients by surgery on menstrual cycle days 0–7 (group 1), days 8–15 (group 2), and after day 15 (group 3).

Table 3 Adjusted HR for death from breast cancer: overall and by stage

Stage[a]	Menstrual cycle interval	Adjusted HR	95% CI	P[b]
All (n = 239)[c]	Group 1	1.29[d]	0.76–2.19	0.34
	Group 2	1.41[d]	0.89–2.23	0.15
	Group 3	1.00[d]		
I (n = 48)	Group 1	1.27[e]	0.15–10.71	0.82
	Group 2	0.98[e]	0.12–8.12	0.99
	Group 3	1.00[e]		
II (n = 154)	Group 1	1.14[f]	0.58–2.25	0.70
	Group 2	1.56[f]	0.92–2.63	0.10
	Group 3	1.00[f]		
III, IV, or no recorded stage[g]	Group 1	1.21	0.49–2.98	0.68
(n = 51)	Group 2	1.29	0.50–3.32	0.60
	Group 3	1.00		

[a] Based on breast cancer staging criteria recommended by the American Joint Committee on Cancer (1988; Ref. 28).
[b] Based on a Wald test derived from a Cox proportional hazards model testing the null hypothesis (HR = 1.0).
[c] Number does not sum to 262, because the model was run using only cases with complete data.
[d] HR adjusting for age, stage, tumor size, grade, and node involvement.
[e] HR adjusting for age.
[f] HR adjusting for age, tumor size, grade, and node involvement.
[g] Women with stages III or IV and no recorded stage were assessed as one group because of their similar survival. When women for whom stage was not recorded were excluded, the estimates did not change significantly (data not shown).

and node involvement. This observation may imply that a certain level of tumor burden must be present for timing of surgery during the menstrual cycle to have an effect.

A survival difference among women with stage II disease but not among women with stage I or stage III and IV disease is plausible, because timing of surgery is likely to affect those women with the greatest variability in survival. Survival for women with stage I disease tends to be uniformly superior. Conversely, survival for women with late-stage disease (*i.e.*, stages III and IV) tends to be poor. Thus, among women with stage I, III, and IV disease, an association between survival and the timing of surgery might not be detected because survival rates are less variable.

Table 4 Adjusted HR for death from breast cancer for women with stage II disease by axillary lymph node status

Node status	Menstrual cycle groups	Age-adjusted HR[a]	95% CI	P[b]
Positive (n = 96)	Group 1	1.08	0.47–2.49	0.86
	Group 2	1.57	0.82–3.03	0.17
	Group 3	1.00		
Negative (n = 58)	Group 1	1.12	0.35–3.62	0.85
	Group 2	1.20	0.45–3.20	0.72
	Group 3	1.00		

[a] HR adjusted for age, tumor size, and grade.
[b] Based on a Wald test derived from a Cox proportional hazards model testing the null hypothesis (HR = 1.0).

For women whose breast cancer has already reached a critical level of tumor burden by the time of diagnosis (*e.g.*, stage II disease with node involvement), processes that increase tumor burden and thus, confer decreased survival may be stimulated more by surgery at certain times during the menstrual cycle (*i.e.*, mid-to-late follicular phase) than at other times. Lower NK cell activity has been observed for breast cancer patients relative to healthy controls, particularly among premenopausal rather than postmenopausal women (4) and for healthy controls in the follicular phase relative to those in the luteal phase (3, 4). These observations suggest that diminished immune function during the follicular phase may reduce the body's defense against metastatic cell growth.

There are limitations to our retrospective study with a modest sample size. Studies in which hormone levels are measured could provide further insights into the postulated association. Whereas a randomized controlled trial would be the ideal way to resolve this important issue, the wide variety of clinical treatments in use today would complicate the design and conduct of such a study, and many would be hesitant to delay surgery to achieve a balanced randomization by menstrual cycle day.

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