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Original Paper

Lack of Correlation between Timing of Surgery in Relation to the Menstrual Cycle and Prognosis of Premenopausal Patients with Early Breast Cancer

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In a retrospective cohort of a randomised study of adjuvant endocrine, chemotherapy and chemo-endocrine therapy, we investigated the correlation between timing of mastectomy and relapse-free survival (RFS) and overall survival (OS) in 721 premenopausal patients with early breast cancer. The median follow-up was 10.1 years (range: 6.1–19.1 years). We grouped the patients by three kinds of classification according to Badwe, Senie, and Hrushesky. The logrank test after the Kaplan–Meier curves showed that there were no significant differences between the categorised menstrual phase in cycle and RFS or OS, except for RFS using Badwe's classification, where the patients whose timing of operation was in the follicular phase had a better RFS compared with those in the luteal phase. These were confirmed by the Cox proportional hazard model. These results suggest that a positive result might be a chance finding, dependent upon the cut-off levels in the menstrual cycle. © **1999 Elsevier Science Ltd. All rights reserved.**

Key words: breast cancer, prognostic factor, menstrual phase, premenopausal, timing of surgery
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INTRODUCTION

THE INCONSISTENCY and variability in the many reports on the correlation of timing of surgery in relation to the menstrual cycle and outcomes of premenopausal operable breast cancer patients have made its prognostic significance uncertain. Hrushesky and colleagues [1], Badwe and coworkers [2] and Senie and colleagues [3] have shown that based on their own classification of the phase in menstrual cycle, the relapse-free survival (RFS), or overall survival (OS) are dependent on the cut-off points. However, these prognostic effects of the proposed classifications were confirmed or not by many others [4–9]. McGuire and coworkers [10] and more recently Sauerbrei and Jaeger [11] have criticised the conflicting results from a methodological point of view: arbitrary cut-off points of timing of surgery in relation to the menstrual cycle; and a relatively small number of patients included in the individual studies (41–562 patients included). Recently, Hagen and Hrushesky [12] reviewed 32 retrospective studies including 9665 patients and they could not conclude whether the menstrual timing of biopsy and/or resection of breast cancer impacts upon outcomes. The purpose of this study was to investigate retrospectively the effect of different cut-off points of the menstrual cycle at the time of surgery on the RFS and OS of the patients.

PATIENTS AND METHODS

Classification of timing of mastectomy during menstrual cycle

The first day of menstruation (bleeding) was designated as day 0. According to the day of surgery during the menstrual cycle, we determined the cycle groups based on the definitions of Badwe and colleagues [2], Senie and coworkers [3] and Hrushesky and colleagues [1]. Namely, according to Badwe's definition, patients were separated into two groups: patients who were operated upon on days 3–12 after the last menstrual period (LMP) and those on days 0–2 or 13–32. Senie's definition was that the menstrual phase was separated into the follicular and the luteal phase by the putative time of ovulation 14 days after LMP (that is days 0–14, and days

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15–36). Hrushesky and colleagues defined as mid-cycle those whose date of surgery was on days 7–20, and as perimenstrual those on days 0–6 or 21–36. The menstrual cycle information was obtained from a specified questionnaire at admission. Almost all patients did not use the oral contraceptive pill during the study period because these drugs have not been approved in Japan.

Patient population

The patients included in this study were a subset of the population of a randomised controlled study on adjuvant treatment [13]. Based on oestrogen receptor (ER) and menopausal status, operable breast cancer (UICC stage I, II, III-A) patients were randomised for adjuvant endocrine therapy, chemotherapy and chemo-endocrine therapy, and the RFS and OS were compared. In premenopausal patients, the following treatments were administered: tamoxifen (TAM) 20 mg/day for 2 years following oophorectomy (OVEX) (TAM + OVEX); chemotherapy with mitomycin-C (MMC) 0.06 mg/kg intravenously (i.v.) on days 1 and 2, followed by intermittent oral cyclophosphamide (CPA) 100 mg/day for 2 years; or the combination of MMC + CPA + TAM. 1579 patients entered the trial between September 1978 and December 1991, of which 837 were designated premenopausal. In this study, women were considered premenopausal when menstruation was confirmed at least 12 months before the day of surgery. When a patient younger than 51 years had undergone hysterectomy with at least one ovary remaining, we included the patient in the premenopausal group.

All patients were followed-up to the end of October 1997, with the median follow-up of 10.1 years (range 6.1–19.1 years). The methods of follow-up with clinical assessment of the patients have been described in detail in a previous study [13]. The RFS patients were those without evidence of recurrence of breast cancer, and those who died of other causes were treated as withdrawals.

Table 1. *Distribution of patients in a randomised trial according to definitions of menstruating phase*

	No. of patients
A randomised trial study of adjuvant therapy for early breast cancer (entry: 9, 1978–12, 1991)	1579
Premenopausal patients	837
Badwe's definition:	
Definitively menstruating	705
Follicular (days 3–12)	244
Luteal (days 0–2/13–32)	461
Delayed menstruation (perimenopausal)	86
Unknown	46
Senie's definition	
Definitively menstruating	721
Follicular (days 0–14)	353
Luteal (days 15–36)	368
Delayed menstruation (perimenopausal)	70
Unknown	46
Hrushesky's definition	
Definitively menstruating	721
Perimenstrual (days 0–6/21–36)	376
Peri-ovulatory (days 7–20)	345
Delayed menstruation (perimenopausal)	70
Unknown	46

Statistical analysis

The Wilcoxon's rank-sum test or the chi-square method were used to test for difference in the background factors of the patients, with the SAS system version 6.10 for Macintosh [14]. The RFS and OS curves were made by the Kaplan–Meier method, and were evaluated by the logrank method. A multivariate analysis with the Cox proportional hazard model was applied to the analysis of prognostic factors for RFS or OS including the menstrual cycle [14].

RESULTS

Because of the different classifications, there were small differences in the number of patients who were defined as definitively menstruating among the three categories (Table 1, that is 705 by the Badwe's, 721 by Senie's and Hrushesky's definitions). Variable numbers of patients with delayed menstruation by each definition (those whose periods of menstruation were shown to be longer than the defined menstrual period, that is longer than 36 days in Senie's and Hrushesky's, and longer than 32 days in Badwe's definition), and 46 with unknown menstrual status (mainly hysterectomy with at least one ovary remaining, and data deficit) were excluded from further analyses.

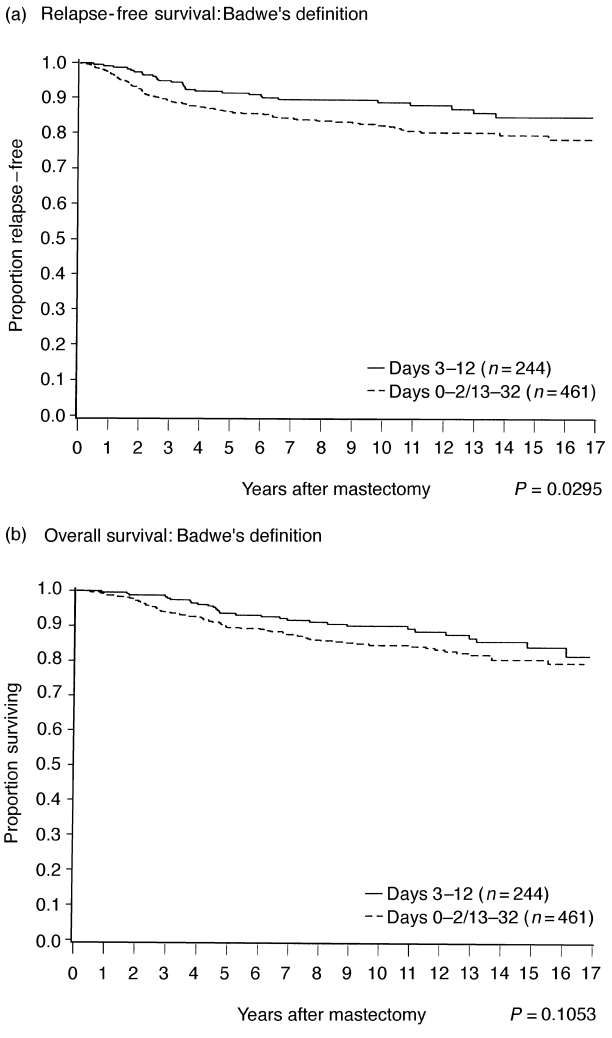

Figure 1. Relapse-free (a) and overall survival (b) curves of premenopausal early breast cancer patients according to the menstrual phase defined by Badwe and colleagues.

Patients' characteristics, in terms of their defined menstrual phase, are shown in Table 2. No statistically significant differences were noted between the two individual groups of each of the three classifications.

For patients whose surgery occurred during the follicular phase, as defined by Badwe and colleagues their RFS was statistically significantly better than those operated upon in the luteal phase (Figure 1a; $P = 0.0295$), although for node-positive patients, this difference was not observed ($P = 0.1332$; data not shown). There was no significant difference between the groups for OS ($P = 0.1053$, Figure 1). There were no significant differences in RFS and OS between the groups defined by Senie and coworkers (Figure 2), and Hrushesky and colleagues (Figure 3).

A multivariate analysis using the backward elimination procedure of the Cox's proportional hazard model indicated that the menopausal phase by Badwe's definition significantly affected RFS but not OS of the patients (Table 3). Other classifications of the menstrual cycle (Senie and coworkers or Hrushesky and colleagues) were not significant for the prognosis of the patients.

Table 2. Background factors of premenopausal patients with early breast cancer according to menstrual phase during operation

	Menstrual phase					
	Badwe's definition		Senie's definition		Hrushesky's definition	
Covariate	Days 3–12	Days 0–2/13–32	Days 0–14	Days 15–36	Days 0–6/21–36	Days 7–20
n	244	461	353	368	376	345
Age (years)						
–34	19	45	27	38	39	26
35–39	54	88	74	74	73	75
40–44	91	149	131	111	139	103
45–49	63	149	96	120	102	114
50–	17	30	25	25	23	27
		($P = 0.3994$)†		($P = 0.7661$)†		($P = 0.1119$)†
Stage						
I	61	114	92	85	94	83
II	144	285	211	232	229	214
III	39	62	50	51	53	48
		($P = 0.6742$)†		($P = 0.5443$)†		($P = 0.8572$)†
Tumour size (cm)						
≤2.0						
≤3.0	71	138	109	104	111	101
3.1–4.0	74	150	107	128	124	111
4.1–5.0	53	88	74	68	75	68
≥5.1	46	85	63	68	66	65
		($P = 0.6096$)†		($P = 0.7889$)†		($P = 0.7737$)†
Histology						
Papillotublar	112	220	162	177	175	164
Solid-tubular	78	141	114	112	124	102
Cirrhous	36	81	56	63	61	58
Special	18	19	21	16	16	21
		($P = 0.241$)⋆		($P = 0.712$)⋆		($P = 0.589$)⋆
Node metastasis						
$n = 0$	135	249	195	197	197	195
$n = 1$–3	76	136	108	108	122	94
$n = 4$–10	21	48	32	40	34	38
$n = 11$–	12	28	18	23	23	18
		($P = 0.3990$)†		($P = 0.4849$)†		($P = 0.2035$)†
ER						
Positive	133	255	198	202	209	191
Negative	97	183	137	147	151	133
Unkown	14	23	18	19	16	21
		($P = 0.910$)⋆		($P = 0.951$)⋆		($P = 0.523$)⋆
Mastectomy						
Radical	123	230	179	184	195	168
Extended	111	220	164	173	168	169
Modified	10	11	10	11	13	8
		($P = 0.568$)⋆		($P = 0.922$)⋆		($P = 0.302$)⋆
Adjuvant therapy						
OVEX + TAM	43	90	67	72	75	64
MMC + CPA	104	183	142	150	155	137
MMC + CPA + TAM	97	188	144	146	146	144
		($P = 0.711$)⋆		($P = 0.921$)⋆		($P = 0.718$)⋆

⋆Chi-square test. †Wilcoxon's rank-sum test. OVEX, oophorectomy; TAM, tamoxifen; MMC, mitomycin-C; CPA, cyclophosphamide.

DISCUSSION

When three different types of classification of menstrual timing of surgery were applied to the survival analysis, only one of the definitions influenced RFS. On the basis of Badwe's classification, contrary to their original report [2], we showed that patients who were operated upon in the follicular phase had a significantly better RFS than those in the luteal phase, with a non-significant difference in the OS curves. Jaeger and Sauerbrei [6] indicated a similar trend, but without a significant difference.

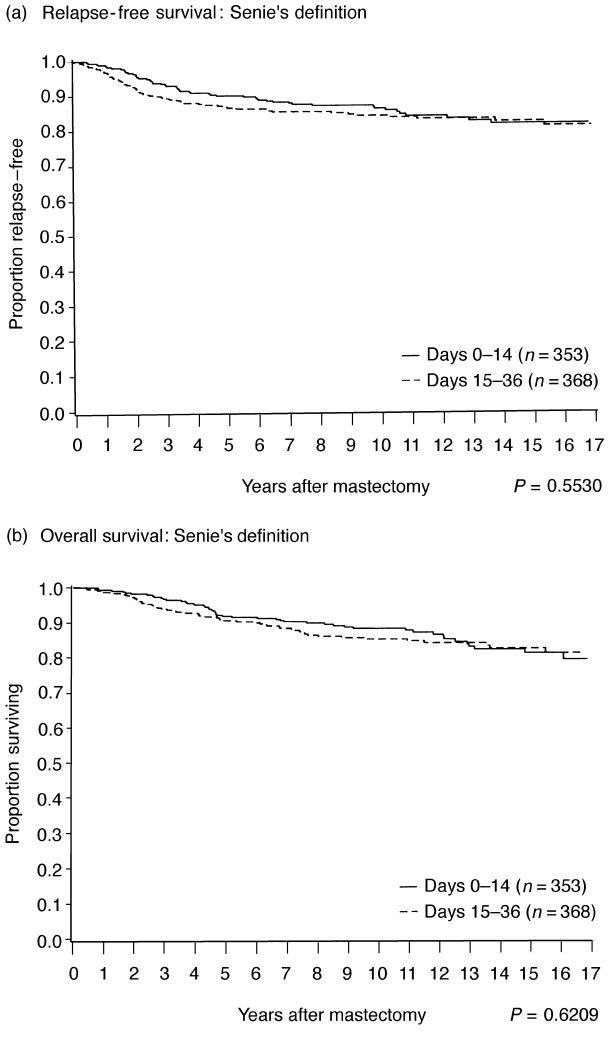

Figure 2. Relapse-free (a) and overall survival (b) curves of premenopausal early breast cancer patients according to the menstrual phase defined by Senie and coworkers.

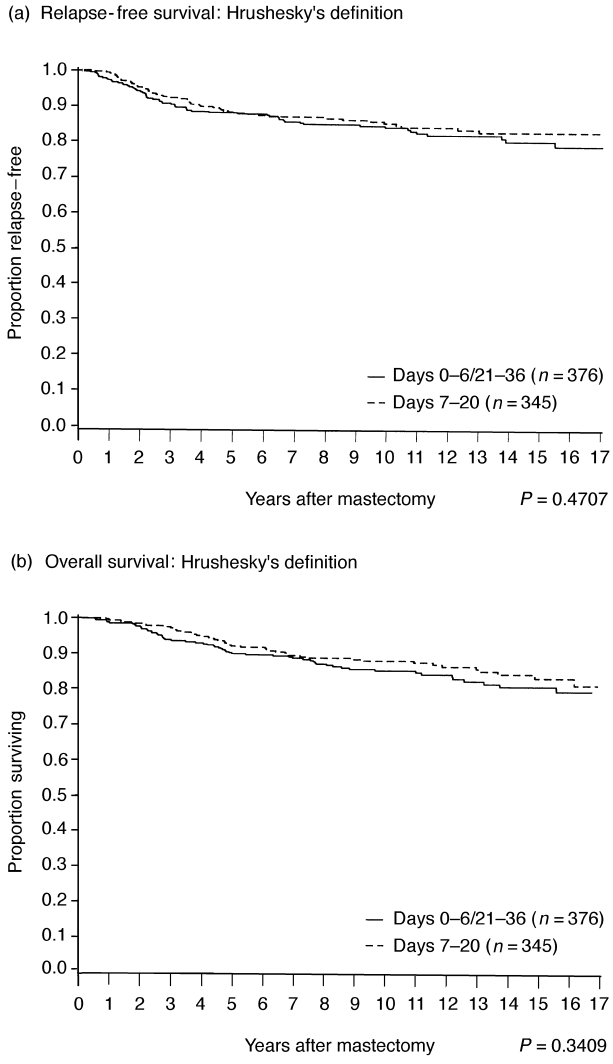

Figure 3. Relapse-free (a) and overall survival (b) curves of premenopausal early breast cancer patients according to the menstrual phase defined by Hrushesky and colleagues.

Table 3. A multivariate analysis of prognostic factors including menstrual phase at surgery in premenopausal early breast cancer patients

Covariate*	Badwe's definition	Senie's definition	Hrushesky's definition
Recurrence (HR with 95% CI)			
Age	–	0.967 (0.935–1.000)	–
Lymph node metastasis	1.105 (1.084–1.125)	1.108 (1.087–1.129)	1.107 (1.086–1.128)
Tumour size	1.233 (1.108–1.373)	1.211 (1.088–1.349)	1.228 (1.102–1.369)
Menstrual phase	1.635 (1.056–2.525)†	–	–
Death (HR with 95% CI)			
Age	–	–	–
Lymph node metastasis	1.101 (1.080–1.122)	1.101 (1.080–1.122)	1.101 (1.080–1.122)
Tumour size	1.225 (1.099–1.364)	1.231 (1.106–1.371)	1.233 (1.107–1.373)
Menstrual phase	–	–	–

*Other variables included were non-significant (stage, oestrogen receptor, histological type, mastectomy type, and adjuvant therapy). †$P = 0.0265$. HR, hazard ratio with 95% confidence interval (CI).

According to the definitions of Senie and coworkers [3] and of Hrushesky and colleagues [1], there were no significant differences in the RFS or OS between the follicular phase and the luteal phase or between the perimenstrual and the periovulatory phases. The same trends were clearly confirmed by Cox's regression model analyses. These results suggest that the effect of menstrual timing of mastectomy on the prognosis of patients depends on the cut-off level of the cycle. This is what McGuire and colleagues [10] suggested, i.e. that a positive association may be spurious and due to chance alone. Jaeger and Sauerbrei [6] also denied the importance of the effect on prognosis.

Badwe and colleagues [2] and Senie and coworkers [3] showed that the correlation between timing of operation and prognosis was mainly present in node-positive patients. In our study, in node-positive patients there were no significant differences for all three classification systems. Although our study is one of the largest reported in the literature, the absence of statistical differences may be due to the type II (β) error because of a small number of positive events, as Japanese patients generally have a better prognosis than those in Western countries.

If elevated levels of unopposed oestrogens stimulate the cell growth and metastasis of breast cancer at the time of surgery depending on the menstrual cycle, we should directly compare oestrogen and progesterone or gonadotropin levels. Badwe and colleagues [15] found that only in node-positive premenopausal patients was higher progesterone levels associated with significantly better survival. However, there was no relationship between oestradiol level and OS. Recently, Silvestrini and colleagues [16] noted that no significant change in ^{3}H-thymidine labelling index (TLI) was observed within the cycle on the overall series, in node-negative or node-positive cancers, or in any of the subgroups defined by steroid receptor status. Other authors have shown differing results on the relationship between indices of cell proliferation in menstrual timing and the outcomes [17,18].

Several studies have indicated that not the mastectomy but rather the tumour excisional biopsy may be influenced by oestrogen changes during menstruation [3]. In our study, a very small proportion of tumours were biopsied before the time of the main surgery. As shown in Table 2, 37 of 705 (5.2%) in Badwe's definition, or 37 of 721 (5.1%) in Senie's or Hrushesky's definitions were excised tumours in other hospitals at various time points before surgery (indicated as 'ER-unknown' in Table 2). Other cancers were biopsied just before the operation (frozen section biopsy) or directly mastectomised in our hospital without any other direct invasion to tumours. Even when those 37 patients were excluded from the analyses, no differences were noted.

In conclusion, it is unlikely that the menstrual timing of surgery has a great impact on the prognosis of breast cancer in menstruating patients. In order to end this rather sterile debate, aside from ongoing prospective studies [12], we propose the following: an overview analysis with raw data of published as well as unpublished data, such as the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) analyses [19] in randomised trial studies to minimise selection and publication errors; and the definition of the menstrual phase not only by the days from the last menstruation, but by hormonal measurement status, for example oestradiol and follicle stimulating hormone (luteinising hormone) at the time of operation.

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