

## ORIGINAL ARTICLE

### Timing of Breast Cancer Surgery During the Luteal Menstrual Phase May Improve Prognosis

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DURING the past 6 years, there has been debate in the literature about the value of timing of breast cancer surgery in relation to the menstrual cycle, since Hrusheshky and co-workers described an influence of estrogens upon experimental metastasis, and reported fewer breast cancer recurrences in women resected during the periovulatory stage of the cycle.<sup>1,2</sup> Larger retrospective studies of menstrual timing have failed to confirm Hrusheshky's original report of only 41 cases, but have indicated instead that late luteal timing of surgery improves recurrence-free prognosis after 10 years several-fold, when compared to procedures performed in the follicular phase. Interpretation of mammograms in menstruating women is more difficult than post-menopause, and often several biopsies may be required to establish a positive diagnosis. Nevertheless, women aged 40-50 have a better life-time prognosis than younger or older women.<sup>3</sup> This group accounts for 40% of years of life annually lost from breast cancer, although only about 15% of breast cancers are detected pre-menopause.<sup>4</sup>

Because menstrual surgical timing is a simple method of improving surgical end-results, we have summarized the currently available reports, up to February 1995 in the Index Medicus. These include 5,353 patients in whom recurrence-free survival was determined after 5-15 years, whose operations were performed during the follicular or luteal cycle phases. Ovulation was generally thought to be on day 13 or 14 after the onset of the last menstrual period. Some reports included day 0-2 along with the luteal phase which at times persisted until day 39.

#### RESULTS:

Most node-negative breast cancer patients today have an excellent prognosis when mammography has detected disease, since the tumors are often less than 2.0 cm in size. They constitute as many as 66-84% of cases in some large series. After 10 years 80% of patients with neoplasms smaller than 2.0 cm continue to be free of cancer, so that there is little room for

further improvement in survival, unlike women with larger primaries.

In the entire series of 20 reports published thus far, there was an overall mean 5% increase in disease-free survival after luteal surgery compared to resections during the follicular phase ( $p=.02$  by Wilcoxon signed ranks test (2-tailed). Many reports did not separate node-negative from node-positive cases in calculating prognosis, and are listed in Table 1. These studies found an insignificant change in survival between luteal or follicular timing of surgery.<sup>5-17</sup> In the largest of the series reported in Table 1, 67% of the cases were node-positive, suggesting that many had not been detected by mammography which has not as yet been systematically utilized in Germany for screening the population.<sup>15</sup> These patients all received 3-6 cycles of CMF adjuvant chemotherapy, in addition to 41 cases given radiotherapy, or Tamoxifen in 41 cases. In contrast, the most recent and only prospective study of menstrual timing reported from Spain included 84% of patients with negative lymph nodes.<sup>17</sup>

The remainder of the cases in which nodal involvement was specified in the follow-up of surgical timing are shown in Table 2.<sup>18-25</sup> Many of the large series also indicated the survival of receptor-positive versus receptor-negative cases. Only 5% overall improvement in survival was seen in the negative-node cases, while the node-positive cases exhibited a  $31\% \pm 3\%$  (SE) mean benefit 5-15 years after luteal surgery. As a result, including both positive and negative lymph node cases in Table 2, the mean overall benefit was  $+15\% \pm 2\%$  (SE), significant at  $p=.05$  by Wilcoxon test.

Patients with less favorable prognosis due to loss of estrogen and/or progesterone receptor function, which include nearly three-quarters of those in this age group also had improved prognosis after luteal surgery, possibly even better than the rest with nodal involvement and posi-

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**TABLE 1.**  
Prognosis after luteal versus follicular timing of breast cancer surgery: lymph node status unspecified

Ref.	No. pts.	Disease-Free Survival (%)			Duration (Years)	P	Remarks
		Luteal	Follicular	Diff.			
5	217	52	62	-10	10	n.s.	
6	205	65	62	+3	10	n.s.	Overall survival
	108	73	67	+6	10	n.s.	2 Hospitals
7	165	78	60-72	+6-18	2-10	n.s.	Hormone assay used for ovulation date
8	125	55	45	+10	12	n.s.	
9	225	44	54	-10	12	n.s.	
10	150 (11*)	65 (100)	35 (0)	+30 (+100)	6 (5)	.001	1985-1990 patients; (needle biopsy* time most important)
11	143	50	68	-18	10	.03	Overall survival
12	132	48	53	-5	11	n.s.	
13	89	56	71-75	-5-11	6	n.s.	Serum hormones for date of ovulation
14	63	34	24	+10	8	n.s.	
15	462	55	56	-1	6	n.s.	33% neg. 1.n.
16	382	?	?	?	?	n.s.	
17	223	?	?	?	4	n.s.	Prospective study, 84% negative 1.n., 97% adjuvant chemotherapy

2,689 cases; Overall benefit

+2%

n.s.

**TABLE 2.**  
Prognosis after luteal versus follicular timing of breast cancer surgery: lymph node status specified

Ref.	No. pts.	Disease-Free Survival (%)			Duration (Years)	P	Remarks
		Luteal	Follicular	Diff.			
18	283	71	57	+14	10	.02	Surgery on d20-30 had 5x better prognosis as Rx on d7-14.
	node neg.	75	73	+2	10	n.s.	
	node pos.	62	39	+23	10	.02	
19	249	84	54	+30	15	.001	1975-1985 pts; best results d30-32; d6-8 surgery 6x worse.
	node neg.	89	82	+7	15	n.s.	
	node pos.	81-85	30-39	+46-51	15	.001	
20	385	57	56	+1	10	n.s.	Overall survival Overall survival
	node pos.	91	91	0	5	n.s.	
	node pos.	74	76	-2	5	n.s.	
21	96	72	40	+32	10	.002	
	node pos.	80	30	+50	10	.009	
22	84 (These cases from 21)	88	52	+36	10	.02	Estrogen receptor pos. Estrog. receptor neg. Progesterone receptor pos. Progesterone receptor neg.
		76	33	+43	10	.009	
		87	60	+27	10	.06	
		76	13	+63	10	.001	
23	1175	70	63	+7	10	.006	Surgery on d28-35 gave best results, d7-14 5x worse prognosis.
	node neg.	76	63	+13	5	.006	
24	210	42	32	+10	15	.05	Overall survival 2x better if serum prog. over 1.5 ng/ml.
	node neg.	84	78	+6	15		
25	266	?	?	?	?	n.s.	2-step surgery gave best prognosis p=.01
	node neg.						
						.002	Estrogen receptor pos.
						.01	Estrogen receptor neg.
						.003	Progesterone receptor pos.
						n.s.	Progesterone receptor neg.

2,664 cases; overall benefit  
Negative Lymph nodes  
Positive Lymph nodes

+15% .05  
+5 ± 2 SE n.s.  
+31% ± 4 SE .05

2-tailed Wilcoxon  
2-tailed Wilcoxon

tive receptors. Many of these reports attained a high degree of statistical significance. If confirmed, this would suggest that survival benefit was greatest for women with the poorest prognosis.

Today more women are receiving preoperative needle biopsies. Two reports observed that the timing of needle biopsy was the critical prognostic factor, rather than the date of surgery later. Follicular-phase needle biopsy in 6 cases resulted in recurrence of cancer in all within 2½ years; 5 patients biopsied during the luteal phase remained free of disease after 5 years, in a series where the overall relapse-free survival was about 65%.<sup>10,25</sup>

Four reports from major cancer treatment centers provided prognosis according to the estimated day of the menstrual cycle that surgery was performed. Three of the four found a 5-6 fold increase in risk of recurrence or death after 10 years for procedures carried out during the second week of the cycle, when ovarian estrogen secretion reached its peak. The nadir of risk in all three reports came during the fourth week or later in the cycle when estrogen secretion was least and progesterone secretion maximal from the corpus luteum.<sup>18,19,23</sup> The fourth major center reported the smallest number of cases, finding some increase in mortality after follicular surgery, but little improvement after luteal surgery.<sup>6</sup> (Figures 1 & 2)

## DISCUSSION:

It is clear that there are two conflicting sets of reports concerning the value of menstrual timing of breast cancer surgery. Many of the reports in Table 1 lack sufficient numbers of patients for statistical significance, and do not provide data on node involvement in relation to survival, or estrogen or progesterone receptor activity. All retrospective series also suffer from the great variability in the duration of the menstrual cycle, which require an objective method of determining the date of ovulation for accuracy of determining the luteal phase.<sup>13,24</sup>

In the largest case series reported from the Milan National Cancer Institute in Table 2 there was only a 7% overall survival benefit of luteal surgery, with nearly two thirds having negative lymph nodes. This improvement in survival was significant at  $p=.006$ . The high proportion of patients with negative lymph nodes in this series, almost twice that of the largest series of cases reported in Table 1, suggests that earlier

detection procedures were better in Italy than for the German Breast Cancer Study Group.

Adjuvant chemo-or hormonal therapy with Tamoxifen were administered to the great majority of node-positive cases, and also in some cases to node-negative patients.<sup>17</sup> Adjuvant chemotherapy with cytoxan, methotrexate and fluorouracil increased survival by 29% after 19 years in node-positive cases, which might obscure the differences in prognosis originating from menstrual surgical timing for some time.<sup>26</sup> Tamoxifen has similar potentialities in prolonging disease-free survival in receptor-positive patients.

The most prevalent theory as to a mechanism for the menstrual effect relates to the number and activity of lymphocytes which have been classified as "natural killer" (NK) cells. These are considered as first line of immune defense against bacterial infection and tumor metastasis, owing to their attraction to immunologically "foreign" antigens. Their numbers and activity are suppressed by estrogen therapy,<sup>27</sup> and reach a nadir along with macrophage activity during the follicular phase of the menstrual cycle.<sup>28,29</sup> Estrogens stimulate release of proteases like Cathepsin D and plasminogen activators from human ER-positive breast cancer cells,<sup>30,31</sup> thereby promoting metastasis through plasmin-mediated destruction of fibrin, and indirect activation of collagenases.<sup>32</sup> Estrogens also stimulate production of insulin-like growth factors (IGF) by breast cancers, increasing proliferation rates and reducing patient survival rates.<sup>33,34</sup>

Tamoxifen blocks these estradiol-induced activities and increases human NK activity *in vitro* and *in vivo*.<sup>26,34</sup> Progesterone acts as a physiologic antagonist of estradiol, by stimulating enzymes in cancer tissue that reduce estradiol to the far less potent estrone, and by reducing nuclear and cytoplasmic ER and PR concentrations. Progesterone also reduces tumor biosynthesis of EGF and other growth factors.<sup>35</sup>

Breast cancers are infiltrated by lymphocytes (including NK cells) in 19-24% of ER-positive and ER-negative tumors respectively. This percentage doubles when there is tumor invasion of lymphatics, which is associated with marked follicular lymph node hyperplasia in up to 58% of regional lymph nodes in breast cancer. Estrogen receptor-negative tumors are also associated with the development of delayed type hypersensitivity to autologous tumor extracts,

indicating that the more undifferentiated tumors with worse prognosis are likely to provoke an immunological host response.<sup>32</sup>

An immediate NK cells response to the dissemination of tumor cells at the time of biopsy or resection could probably localize and destroy small numbers of invading cells, as observed by Hrushesky in his experimental tumor model.<sup>1,2</sup> Larger inocula would have less chance of destruction.

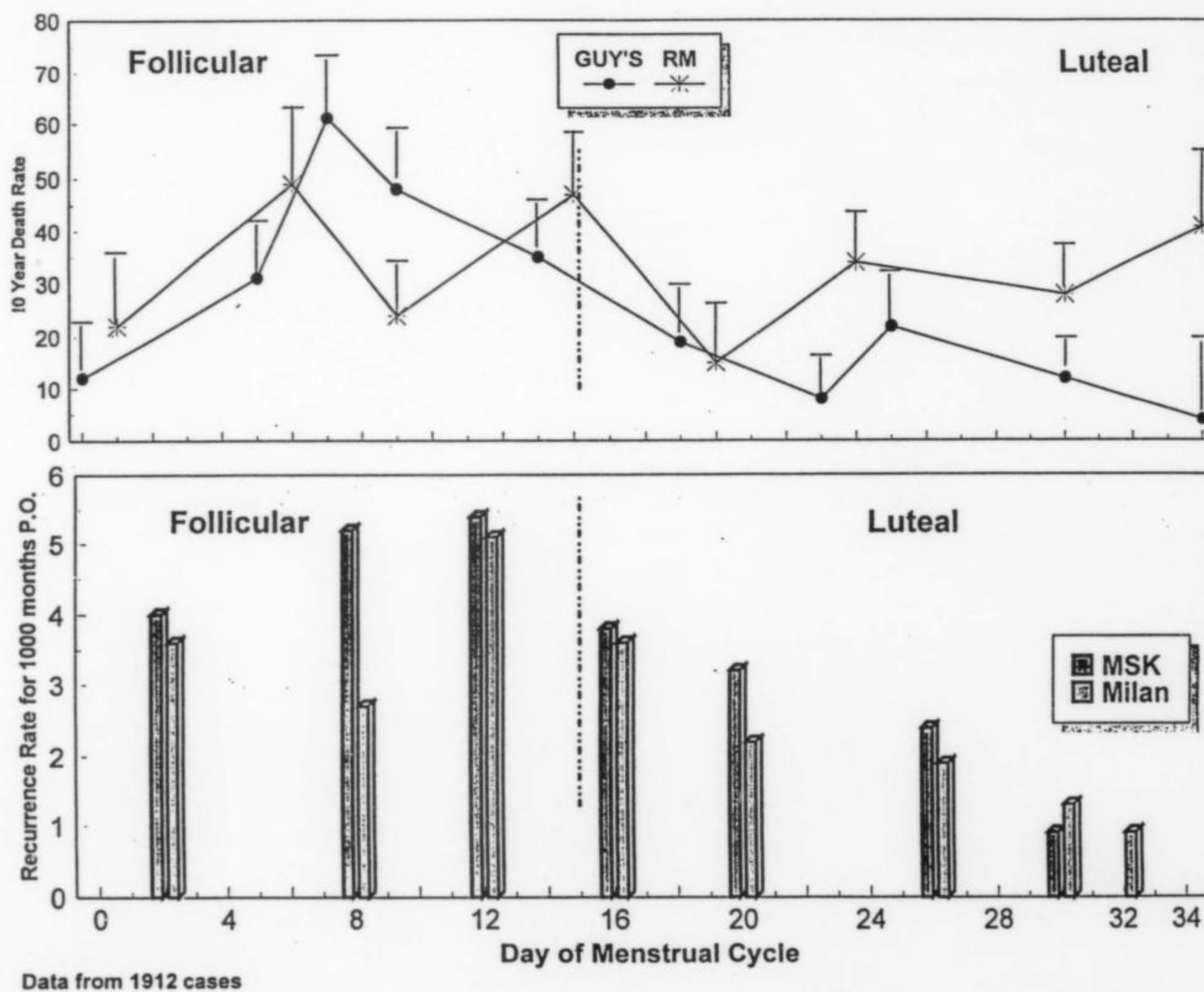
These observations correlate well with the clinical data in Table 2 and the differences observed in 10-year survival shown in Figures 1 and 2. The marked differences in prognosis after needle biopsy in the luteal and follicular phases suggests that these small tumor cell disseminations are most effectively destroyed.<sup>10</sup> Improved prognosis after luteal surgery occurring with ER-positive and ER-negative tumors<sup>22,25</sup> is consistent with an immunological mechanism affecting invasive cancers with high predilection of distant metastasis.

Natural killer cell activity is depressed by the presence of breast cancers.<sup>36</sup> Daily oral ingestion of a new investigational drug with minimal systemic toxicity, Linomide, augments NK activity in healthy subjects.<sup>37</sup> If natural killer cells are shown to be important in improving prognosis after surgical treatment in premenopausal women, this drug may possibly augment cell-mediated anti-cancer immunity in these patients as well as postmenopause, with benefit for all women with breast cancer.

Prospective randomized clinical trials are needed to determine the full extent of survival benefit that may result in more accurate determination of ovulation time and the luteal phase of the cycle, and whether indeed prognosis is affected by host immunologic response.<sup>38</sup> Meantime we urge that all Nebraska physicians henceforth record the data of onset of the last menstrual period and/or ovulation of all young women having diagnostic or therapeutic surgical breast procedures. Annually 2,000 new

**FIGURE 1 & 2**

Breast cancer recurrence rate per 1000 months observation (bras), and percent of patients dying of breast cancer (open and solid dots  $\pm$  SD) after 10 years observation, according to day of menstrual cycle of their operation. Derived with permission from ref. 18 (MSK), 19 (Guy's), 6 (RM) and 23 (Milan).



Data from 1912 cases

cases of breast cancer are reported to the Nebraska Cancer Registry, with about 300 premenopausal cases. In a few years a valuable data bank could be assembled dealing with this topic important to our patients welfare.

## SUMMARY

A meta-analysis has been performed of available retrospective reports concerning the 5-15 year disease-free survival of 5,353 premenopausal breast cancer patients operated on either during the follicular or luteal phases of the menstrual cycle. Patients with surgery performed during the luteal phase (d14-23+) had an overall mean 5% benefit compared to those operated on the follicular phase determined by date of onset of their last menstrual period  $p=0.02$  by Wilcoxon 2-tailed test.

When nodal invasion was reported, node-negative patients had a  $5 \pm 2\%$  SEM benefit. Patients with positive nodes had a  $34 \pm 3\%$  SEM increase in survival ( $p=.05$ ), including both estrogen and progesterone-receptor negative as well as positive neoplasms. In 3 of 4 reports from major cancer treatment centers, each containing 249-1175 cases, risk of recurrent cancer and/or death increased 5 to 6-fold after 10 years for women receiving surgery during d7-14 of their cycle, compared to those resected during d21-36. Improvement in prognosis was greatest for patients with the highest risk of recurrence due to node-invasive disease and receptor dysfunction. Several cell-mediated immunologic factors inimical to metastasis are maximal in the luteal phase of the menstrual cycle, including natural killer cell activity. A new drug which augments natural killer cell activity may extend any beneficial survival results to post-menopausal breast cancer patients in the future.

We conclude that accurate menstrual histories should be included in the medical record from now on for all premenopausal women receiving any surgical procedure upon the breast, preferably using an objective method of determining the date of last ovulation. Prospective randomized clinical trials are necessary to determine the full extent of survival benefits of late luteal surgical timing.

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