

REVIEW ARTICLE

Timing of breast cancer surgery in relation to the menstrual cycle – The rise and fall of a hypothesis

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Abstract

It has been claimed that the timing of surgery in relation to the menstrual cycle can significantly influence the prognosis among premenopausal women with primary breast cancer. The literature on the subject is reviewed. The results are heterogeneous, and the quality of the studies is in general low. Many studies suffer from statistical problems concerning small sample sizes and sub-group analyses. In all, the scientific basis for the hypothesis seems weak.

The hypothesis

In 1989 Hrushesky et al. [1] published a study in *The Lancet* based on 42 breast cancer patients, indicating that if surgery was performed around the time of menstruation, the survival was significantly reduced compared with women operated on in the middle of the menstrual cycle. The study was performed based on a hypothesis from animal experiments showing a cyclic variation in risk of surgically related metastatic spread of tumour cells. This was presumed to be mediated through changes in activity of natural killer cells [2]. Subsequent studies were unable to confirm the observation [3–5]. In 1991, Badwe et al. [6] launched a new theory in *The Lancet*. In this study women operated on day 3–12 of the menstrual cycle, in the follicular phase, were observed to have a reduced survival. The new hypothesis was that when surgery was performed in the period of the menstrual cycle associated with high levels of estrogens and low level of progesterone, tumour cells spread during surgery would have better chances of survival and seeding.

Studies on the subject

Literature search

Literature search was performed in Medline using the search words breast cancer, prognosis, and

menstrual cycle. The bibliographic references in all retrieved articles were examined for potential secondary sources.

Studies

A large number of retrospective studies on the prognostic influence of timing of surgery in relation to the menstrual cycle were identified (Table I). In 20 of a total of 35 studies, including the largest on the subject [7], timing of surgery is found to be without prognostic influence. In the remaining 15 studies, 11 are in favour of the current hypothesis that surgery performed in the follicular phase of the menstrual cycle is associated with an inferior prognosis. However, the definition of the follicular phase is not consistent in the studies and four studies find survival to be best when surgery is performed in other periods of the menstrual cycle [1,8–10]. In more studies positive findings are only associated to sub-group analysis [11–13].

Pujol et al. took the advantage of analysing pre-operatively collected blood samples in order to measure the exact phase of the menstrual cycle among 360 women [14]. This method is far superior compared to estimating the menstrual phase based on recorded day of last menstrual period. The study revealed no prognostic influence of timing of surgery.

Table I. Studies on the prognostic effect of timing of surgery in relation to the day of the menstrual cycle.

Reference	Year		Number of patients	Days of menstrual cycle associated with poor outcome
Hrushesky [1]	1989	Single institution record survey	41	0–6, 21–36
Powles [3]	1989	Single institution record survey	81	No relationship
Gelber [4]	1989	Single institution record survey	245	No relationship
Ville [5]	1990	Single institution record survey	279	No relationship
Badwe [6]	1991	Single institution record survey	249	3–12
Low [25]	1991	Single institution record survey	125	No relationship
Rageth [26]	1991	Single institution record survey	224	No relationship
Senie [27]	1991	Single institution record survey	283	7–14
Sigurdsson [28]	1992	Single institution record survey	382	No relationship
Gnant [29]	1992	Single institution record survey	385	No relationship
Sainsbury [8]	1993	Single institution record survey	143	0–2, 13–32
Donegan [30]	1993	Four institution record survey	97	No relationship
Marques [31]	1993	Single institution record survey	63	3–12*
Spratt [9]	1993	Single institution record survey	40	7–20*
Nathan [32]	1993	Single institution record survey	132	No relationship
Corder [33]	1994	Single institution record survey	157	No relationship
Kroman [7]	1994	Nation wide record survey	1,635	No relationship
Wobbles [34]	1994	Single institution preoperative blood samples	89	No relationship
Saad [35]	1994	Three institution record survey	96	1–12
Veronesi [36]	1994	Single institution record survey	1,175	0–14
Jager [37]	1995	Single institution record survey	562	No relationship
von-Minckwitz [11]	1995	Single institution record survey	226	3–12 †
D'eredita [38]	1995	Single institution record survey	133	No relationship
Kurebayashi [39]	1995	Single institution record survey	100	3–12 ‡
Holli [40], 1995	1995	Multi centre record survey	267	1–14*
Stonelake [10]	1995	Single institution record survey	221	0–2, 13–28
Tsuchiya [41]	1996	Single institution record survey	159	No relationship
Toscano [42]	1996	Three institution record survey	254	No relationship
Goldhirsch [12]	1997	Multi centre record survey	1,033	3–12 §
Mondini [43]	1997	Single institution record survey	165	No relationship
Vanek [44]	1997	Single institution record survey	150	No relationship
Chang [45]	1997	Three institution record survey	262	8–15*
Milella [46]	1999	Prospective	248	No relationship
Nomura [47]	1999	Single institution record survey	721	No relationship
Pujol [14]	2001	Prospective based on blood samples	360	No relationship
Love [13]	2002	Prospective randomized	565	1–14**
Takeda [48]	2003	Single institution record survey	36	No relationship

* Result not significant.

† Result only significant among 119 patients operated in a two-step procedure.

‡ Result only significant in univariate analysis.

§ Result only significantly positive among 300 oestrogen receptor negative patients.

**Result only positive among 276 patients receiving oophorectomy and tamoxifen.

Discussion

The literature on whether timing of surgery is of prognostic importance is very confusing. The initial theory on this subject [1], was never widely accepted. The next hypothesis, which is the one most widely debated, is that women operated on at the time in the menstrual cycle with a high unopposed oestrogen level are at increased risk of relapse and death. This theory was launched without any convincing theoretical basis, at a time when another theory was investigated, and the observation may have been made due to chance alone [15]. Some

studies have supported the hypothesis, but the majority have not (Table I).

Furthermore, the studies supporting the hypothesis define different high risk periods of the menstrual cycle (Table I), which suggest that the results may have been data driven, and this may further induces a risk of bias towards positive results [16]. McGuire et al. made an experiment where 675 women with breast cancer from San Antonio Tumor Bank were randomly assigned a day in the menstrual period [15]. They defined 14 fictitious different ways of separating the menstrual cycle. When repeating the experiment 100 times it was possible to identify a

significant high-risk period in 28 cases. This very clearly indicates that moving the high-risk period around may induce the finding of significant results.

Some authors [17–21] who have performed meta-analyses based on the published studies, conclude that the theory of a negative prognostic effect of operation in the menstrual phase with high level of unopposed oestrogen may hold up. However, this way of evaluating a hypothesis is problematic, because of the risk of publication bias. The chance of having a study with a positive result published is much higher than getting a negative study published [22]. Thus, meta-analysis on published material only will overestimate an effect of surgical timing.

In the initial study by Badwe et al. [6] the survival advantage was 30% for patients operated on at the presumed favourable period of the menstrual cycle. However, the study from DBCG failed to support the hypothesis [7]. Due to the large size of this study, the risk of overlooking a therapeutic effect as reported by Badwe et al. would be around 1%.

Anamnestic information on menstrual cycle is an uncertain way of estimating endocrine status of a woman. Furthermore, the majority of patients included in the present studies are more than forty years of age. Thus, they are at the time in life when ovulation and thus the menstrual cycle becomes increasingly irregular and luteal insufficiency occurs. The question as to prognosis and timing of surgery in relation to the menstrual cycle can hardly be further analysed through studies based on information on day of menstrual cycle alone. More evidence has to be collected through well designed prospective studies in which endocrinological status is based on blood tests of the individual woman [19,23]. The only larger study based on such method was negative [14].

In conclusion the evidence of a prognostic effect of timing of breast cancer surgery seems weak. There are huge methodological problems related to many published studies. In an editorial comment by Hortobagyi on the subject he notes that: “If you torture the data enough, it will confess” [24]. However, the present author will not.

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