

Timing of surgery for primary breast cancer with regard to the menstrual phase and prognosis¹

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Key words: breast cancer, menstrual cycle, surgery, unopposed estrogen, progesterone

Summary

The hormonal milieu of the patient at the time of surgery may influence the prognosis of patients with primary breast cancer. Circulating unopposed estrogen is perhaps detrimental, while circulating progesterone may confer a survival advantage. This hypothesis has particular relevance to the timing of surgery in relation to the menstrual cycle. After all, the first 14 days of the menstrual cycle (follicular phase) are characterized by high levels of circulating unopposed estrogen, while circulating progesterone is present during the second 14 days of the cycle (luteal phase). Several retrospective studies have shown that surgery during the follicular phase of the menstrual cycle results in a worse disease-free and overall survival. Randomized controlled trials addressing the effect of timing of surgery or neoadjuvant hormonal therapy on breast cancer mortality are urgently needed to confirm or refute the unopposed estrogen hypothesis. Such trials may provide important insights into the natural history of breast cancer, and a basis for significantly reducing breast cancer mortality.

Introduction

Since ancient times, enthusiasm for the surgical management of breast cancer has waxed and waned [1]. Hippocrates advised against surgery, arguing that patients who have their tumors excised “quickly perish; while they who are not excised live longer” [2]. This notion was discarded by the late 19th century, when Halsted proposed that breast cancer spreads in an orderly fashion through the lymphatics to the regional lymph nodes and then to distant sites [3]. Thus, Halsted believed that extirpation of the primary

tumor, lymphatics, and regional nodes could significantly reduce breast cancer mortality. He described the radical mastectomy, aimed at removing the tumor-containing breast with its ipsilateral axillary contents and pectoral muscles en bloc, as the optimal treatment for primary breast cancer [4]. As a logical extension of the Halsted paradigm, researchers during the first three quarters of this century directed their efforts towards improvements in surgical techniques and experimentation with super-radical operations. For example, the extended radical mastectomy, which incorporated the radical mastectomy with

¹ The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the Departments of the Army, Air Force, or Defense.

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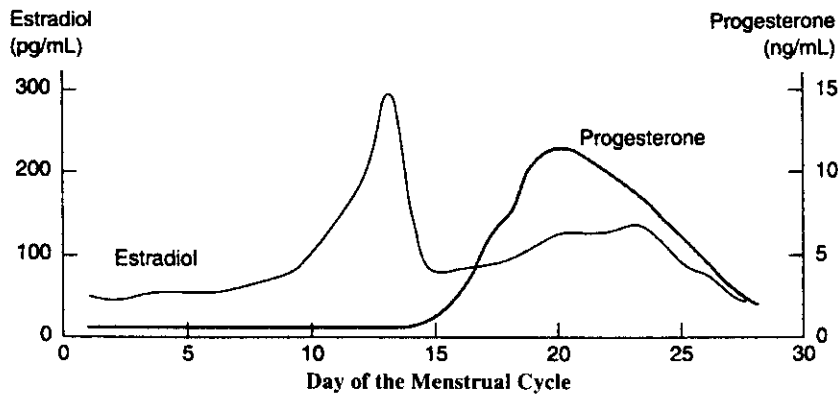


Figure 1. Variations in the levels of estradiol and progesterone during the menstrual cycle. (From [51], with permission.)

extirpation of the internal mammary lymph nodes, was briefly touted as a significant advance in the management of breast cancer [5]. During this era, the treatment of breast cancer was predicated on an anatomical model of disease progression, with little consideration given to the systemic effects of surgery.

Eventually, randomized controlled trials proved that the Halsted paradigm was flawed. When clinical trials compared the radical mastectomy with more conservative procedures, there was no difference in survival between the two groups [6]. Most investigators interpreted these results to mean that surgery had little, if any, impact on breast cancer mortality, and was essential only for the local control of the primary tumor [7]. However, these trials did not compare surgery against untreated controls, and therefore provide no information on the overall effect of surgery on breast cancer mortality. Rather, these trials suggest that the extent of the mastectomy does not influence mortality. In contrast, randomized trials have shown that adjuvant systemic therapy reduces breast cancer mortality by about 25% [8]. This led one prominent surgeon to conclude that the roles of surgery and systemic therapy are now reversed: surgery is the adjuvant therapy, while systemic therapy is the primary treatment of breast cancer [9]!

Surgery and the hormonal milieu

However, the impact of surgery on breast cancer mortality has not been fully elucidated. An excess hazard rate for relapse and death has been reported during the first three years following surgery for breast cancer [10]. This excess hazard of death then falls to baseline levels before showing a second, less dramatic peak some years later. One might interpret this to mean that surgery perturbs the natural history of breast cancer. Additionally, there is evidence that the impact of surgery on breast cancer mortality is influenced by the hormonal milieu of the patient [11]. Circulating unopposed estrogen at time of surgery is perhaps detrimental, while circulating progesterone may confer a survival advantage. Two important observations support this hypothesis. First, the menopausal status of the patient at the time of surgery appears to influence mortality, with perimenopausal women having a particularly poor prognosis [12,13]. The perimenopausal period is characterized by anovulatory cycles and therefore high levels of circulating unopposed estrogen. Secondly, obese postmenopausal women have a worse outcome than do thinner women following surgery for primary breast cancer [14,15]. This effect is probably not the result of a delay in diagnosis among heavier women, in

whom a breast mass might be more difficult to detect. The adverse effect of obesity on recurrence and mortality is independent of other known prognostic factors, such as clinical stage, axillary lymph node status, and histologic grade of the tumor. The main source of estrogen in postmenopausal women is the enzyme aromatase, present in body fat, which converts the inactive precursors of estrogen to the active hormone [16]. Obesity is associated with an excess of body fat, and hence higher levels of circulating unopposed estrogen. Thus, the higher levels of circulating unopposed estrogen at the time of surgery might account for the worse prognosis of obese postmenopausal women.

The timing of surgery in relation to the menstrual cycle is therefore a possible means of reducing breast cancer mortality. After all, the first 14 days of the menstrual cycle (follicular phase) are characterized by high levels of circulating unopposed estrogen, while circulating progesterone is present during the second 14 days of the cycle (luteal phase) (Figure 1). Thus, if circulating unopposed estrogen at the time of surgery is indeed detrimental and circulating progesterone confers a survival advantage, then patients undergoing surgery during the follicular phase should have a worse prognosis than those undergoing resection during the luteal phase of the menstrual cycle. In recent years, this hypothesis has generated considerable controversy.

Hrushesky et al were the first to report that timing of surgery in relation to the menstrual cycle could influence outcome in patients with primary breast cancer [17]. However, the authors did not attribute this effect to circulating unopposed estrogen. In experiments with mice, Hrushesky's group observed that pulmonary metastasis was more frequent following resection of breast cancer during the first half of the estrous cycle, when compared to the latter half [18]. They interpreted this to mean that prognosis was better when resection of the primary tumor was carried out at time of ovulation. On the basis of these findings, the investigators undertook a retrospective study, comparing outcome in 22

patients resected during the perimenstrual period (days 0-6 and 21-36 of the menstrual cycle) with 19 patients resected at midcycle (days 7-20) [17]. The risk of recurrence was significantly less following resection during the midcycle, which seemed to support the notion that surgery at the time of ovulation confers a survival advantage. In this small series of patients, no direct comparison was made between surgery during the follicular phase and the luteal phase of the menstrual cycle. Nonetheless, this study stimulated interest in the timing of surgery, and a flurry of retrospective studies soon followed.

Badwe et al compared resection between days 3-12 after the last menstrual period (LMP) with resection between days 0-2 or 13-32 in patients with primary breast cancer [19]. While these intervals did not conform precisely with the follicular and luteal phases of the menstrual cycle, the study was undertaken with the prior hypothesis that surgery in the presence of circulating unopposed estrogen is detrimental. These authors reviewed the records of 249 patients at the Guy's Hospital in London and found that overall survival and relapse-free survival were significantly worse in patients who underwent resection between days 3-12 after LMP, a period corresponding to high levels of circulating unopposed estrogen ($p < 0.001$). About the same time, Senie et al. reviewed the records of 283 patients at the Memorial Sloan Kettering Cancer Center in New York, and found that the risk of breast cancer recurrence was significantly greater following resection during the follicular phase of the menstrual cycle, when compared to the luteal phase, the hazard ratio being 1.53 (95%CI: 1.02 to 2.29) [20]. To date, the largest retrospective study in support of the unopposed estrogen hypothesis has been that of Veronesi et al from the Tumor Institute of Milan [21]. These authors reviewed the records of 1175 premenopausal women with primary breast cancer whose date of last menstrual period was known. The risk of recurrence was significantly greater in those patients undergoing resection during the follicular phase of the menstrual cycle, the hazard ratio being 1.329

(95%CI: 1.038-1.631). Thus, in retrospective studies from three large centers, resection during the unopposed estrogen phase of the menstrual cycle has been associated with a worse outcome. In all three studies, the effect was greater in node positive than node negative patients. These studies therefore support the hypothesis that the hormonal milieu of the patient at time of surgery has an impact on breast cancer mortality, and suggest that circulating unopposed estrogen is detrimental.

Conflicting data

Several groups have confirmed these results, and others have not [22,23,24]. The largest study that has failed to show any relationship between timing of surgery and outcome has been that of Kromen et al, who reviewed the results of 1635 premenopausal breast cancer cases from the Danish Breast Cancer Cooperative Group [25]. In addition, Sainsbury et al of the Yorkshire Regional Cancer Organization reported that surgery during the follicular phase of the menstrual cycle was associated with a better prognosis, results just opposite to those from Guy's, Memorial Sloan Kettering, and NCI Milan [26]. However, in the Yorkshire study, timing of surgery was not an independent prognostic factor in a multivariate analysis.

Several investigators have called attention to the pitfalls of these retrospective studies [27,28]. Information concerning the phase of the menstrual cycle was gathered from patients' charts, and may not be reliable. Women may not accurately recall the exact date of their last menstrual period, and may have late or early ovulation. For example, a woman undergoing surgery after the 14th day would be categorized as in the luteal phase, but may actually be in the follicular phase because of late ovulation. The measurement of serum hormone levels is therefore a more reliable means of ascertaining phase of the menstrual cycle, but only a few investigators were fortunate to have had serum samples available from around the time

of surgery.

Wobbes et al reported the results of 89 premenopausal women with primary breast cancer who had serum samples taken and stored either one day prior to or on the day of surgery [29]. The phase of the menstrual cycle was determined on the basis of 17β -estradiol and progesterone levels, and patients were grouped into one of three categories of the menstrual cycle: follicular, periovulatory, or luteal. After a median followup of 4.1 years, there was no difference in disease-free survival among the three groups. Ville et al reviewed the records of 165 premenopausal breast cancer patients who had serum samples taken and stored the day before surgery [30]. Hormone levels were measured, and the patients were grouped into one of four categories: perimenstrual, follicular, ovulatory, and luteal. There was a trend towards improved survival in patients who underwent tumor resection during the luteal phase, but the results were not statistically significant. Badwe et al retrospectively reviewed outcome in 210 premenopausal women with operable breast cancer who had serum samples taken within 3 days of tumor excision at Guy's Hospital [31]. Serum progesterone levels were measured, and patients were divided into two groups: those having levels >1.5 ng/ml (luteal phase), and <1.5 ng/ml (follicular phase). Among the node negative cases, there was no difference in outcome between the two groups. However, higher progesterone levels were associated with significantly better survival in node positive patients. Subsequently, Mohr et al added an additional 79 cases to Badwe et al.'s cohort of patients [32]. In the expanded cohort of 289 patients with serum samples taken within 3 days of tumor excision, the authors reported significantly better survival in patients with progesterone levels greater than 4 ng/ml. Again, the effect was particularly evident in node-positive patients.

In view of the conflicting results from centers around the world, many investigators have expressed skepticism over any correlation between timing of surgery and prognosis, suggesting that the positive findings are due to chance alone

[33,34]. These investigators argue that, if patients are randomly divided into subsets according to period of the menstrual cycle at time of surgery, one might find, by chance alone, a significantly better prognosis associated with one or more subsets. Could such random subsetting account for the positive findings? This seems unlikely. After all, the studies from the three largest centers reporting positive findings (Guy's, Memorial Sloan Kettering, and NCI Milan) were undertaken with the prior hypothesis that surgery during the unopposed estrogen phase of the menstrual cycle is detrimental. In addition, the magnitude of the benefit is quite large in these studies, and should not be dismissed lightly. What, then, might account for the conflicting reports?

One possible explanation is that, amongst centers, there is considerable variation in the diagnosis and management of breast cancer. For example, breast cancer is sometimes diagnosed by a definitive surgical procedure, such as an excisional biopsy (resulting in the complete removal of the breast mass), and in other instances by less invasive procedures, such as a trucut needle biopsy or fine needle aspiration cytology, followed by a definitive surgical procedure once the histological diagnosis of cancer is established. Thus, the primary breast cancer might be manipulated once (as in the case of excisional biopsy), or twice (if a needle biopsy precedes the definitive surgical procedure). In instances where the primary cancer is manipulated twice, the timing of the needle biopsy may confound the effect of timing of surgery. For example, a patient may undergo a trucut needle biopsy of a breast mass during the follicular phase of the menstrual cycle, followed by a mastectomy during the luteal phase.

When Badwe et al first reported the effect of timing of surgery on outcome, they included only those patients seen between the years 1975-1985, before the advent of trucut needle biopsies at Guy's Hospital [19]. During this period, patients underwent an excisional biopsy as the diagnostic procedure. If cancer was found, an axillary lymph node dissection was undertaken at a later date. Thus, the primary breast cancer was manip-

ulated only once. In 1985, the trucut biopsy was introduced at Guy's Hospital. Therefore, Badwe et al separately studied patients seen at Guy's Hospital after 1985, and compared outcome between follicular and luteal trucut biopsies, in women undergoing surgery during the luteal phase of the menstrual cycle [35]. Relapse-free survival was significantly better when trucut biopsy was undertaken during the luteal phase of the menstrual cycle, suggesting that the timing of an invasive diagnostic procedure may indeed confound the effect of timing of surgery. Badwe and Juvekar point out that, in those series reporting a correlation between timing of surgery and outcome, the primary tumor was generally treated with a single procedure: an excisional biopsy as the diagnostic procedure, or frozen section followed by mastectomy [36]. A trucut biopsy or fine needle aspiration of the breast mass was not performed, and the primary breast cancer was therefore manipulated only once.

Prospective studies

In 1994, Fentiman et al conducted a meta-analysis of all published work on the effect of timing of surgery in premenopausal women with primary breast cancer [37]. In their overview of 21 reported studies, the overall effect of timing of surgery was significant ($p=0.02$), with a 16% reduction in the risk of relapse associated with surgery during the luteal phase of the menstrual cycle. This effect was seen despite considerable variation in the diagnosis and management of breast cancer amongst the various centers. Thus, Hrushesky proposes that the question of timing of surgery be submitted to a randomized prospective trial [38]. Ultimately, this may resolve the controversy over timing of surgery, and perhaps provide a basis for significantly reducing breast cancer mortality in premenopausal women. Nonetheless, concerns about such a trial have been expressed [34]. There would often be delays in the primary treatment of breast cancer, and recruitment into the trial might therefore prove

difficult. In addition, as the timing of both the invasive diagnostic procedure and definitive surgery appear to influence outcome, how would one randomize the timing of both procedures? Consequently, there has, thus far, been limited support for a randomized prospective trial. However, some groups have initiated prospective registration studies. The North Central Cancer Treatment Group (NCCTG) has been joined by the National Surgical Adjuvant Breast and Bowel Project (NSABP) in such a study [39]. The phase of the menstrual cycle will be documented by measuring serum hormone levels at the time of surgery, with long-term followup of all registered patients. A similar study has been initiated by the Yorkshire Regional Cancer Organization in England, where phase of the menstrual cycle at the time of operation, use of contraceptives, and types of diagnostic interventions, such as mammography, cytology, and trucut biopsy, will be documented [40]. In addition, serum levels of estrogen, progesterone, luteinizing hormone, and follicle stimulating hormone will be measured, to relate hormonal findings with any observed effects.

A neoadjuvant progesterone trial might also prove useful [41]. Such a trial would test the unopposed estrogen hypothesis and have relevance to both pre- and postmenopausal women. As endocrine therapy is now routinely used to treat benign breast disease, the brief administration of progesterone therapy prior to breast biopsy in a clinical trial setting should not cause concern. Thus, women suspected of having breast cancer on mammography or clinical examination could be randomized to receive either progesterone or placebo before needle biopsy or excisional biopsy. Those patients who have cancer confirmed on biopsy could continue to receive either progesterone or placebo until definitive surgery is performed. As half the premenopausal women in the placebo group would be expected to undergo surgery during the luteal phase of the menstrual cycle (in the presence of circulating progesterone), it might be prudent to measure a progesterone level just before surgery. In premeno-

pausal women, administering progesterone before needle biopsy and surgery may prove far easier than attempting to coincide various procedures with the luteal phase of the menstrual cycle.

Biological mechanism

How might circulating unopposed estrogen at the time of surgery increase mortality, and the presence of progesterone confer protection? This question, of course, remains wide open to speculation. Fentiman and Gregory suggest that the hormonal milieu affects cohesion of the primary tumor [42]. These authors postulate that circulating unopposed estrogen may increase the risk of dissemination of malignant cells during handling of the tumor at time of surgery. Indeed, it has been shown that estrogens lead to cell proliferation and induction of proteases [43]. Thus, circulating unopposed estrogens at time of surgery may promote the shedding of tumor cells into the circulation. In contrast, progesterone has anti-proliferative activity, and may negate the deleterious effect of estrogen [44].

However, circulating unopposed estrogen appears also to be associated with an increased risk of micrometastases, even prior to tumor handling [45]. We retrospectively reviewed the records of 350 patients with primary breast cancer who underwent surgery at the Royal Marsden and St. George's Hospital in London between 1981 and 1986. Bone marrow aspirates were taken just prior to surgery, and the presence or absence of micrometastases in the bone marrow was determined using antibodies to epithelial membrane antigen. Each patient was placed in one of three categories: premenopausal, perimenopausal, or postmenopausal. The perimenopause was defined as the interval from the start of irregular cycles to 2 years after the last cycle, a period associated with anovulatory cycles and therefore with high levels of circulating unopposed estrogen. In a multivariate analysis, the risk of bone marrow micrometastases was 2.5 times greater in the perimenopausal group, compared to the other two

Table 1. Evidence that surgery in the presence of circulating unopposed estrogen is associated with poor outcome in patients with primary breast cancer

Observation	Rationale
<ul style="list-style-type: none"> • Poor outcome in perimenopausal women. • Worse outcome in obese compared to thinner postmenopausal women. • Surgery during the luteal phase of the menstrual cycle associated with better disease-free and overall survival, compared to the follicular phase. 	<ul style="list-style-type: none"> • Anovulatory cycles and therefore high levels of circulating unopposed estrogen. • High levels of circulating unopposed estrogen due to enzyme aromatase, present in body fat, that converts inactive precursors of estrogen to active hormone. • Luteal phase of the menstrual cycle associated with circulating estrogen/progesterone while follicular phase is associated with unopposed estrogen.

groups. We can only speculate as to what might, prior to surgery, promote micrometastases in the presence of circulating unopposed estrogen. Insulin-like growth factor I (IGF-I) certainly merits consideration [46]. Indeed, stimulation of IGF-I expression by estrogens has been reported, and it is a potent mitogen for breast cancer cells. In addition, a decrease in natural killer cell activity has been observed in peripheral blood during the follicular phase of the menstrual cycle, and this could promote micrometastases as well [47].

Gunduz et al and Fisher et al have shown that surgery to remove a primary tumor can stimulate growth of distant metastases, and suggest that this effect is mediated through cytokines released at the time of surgery [48,49]. More recently, the relationship between the primary tumor and micrometastatic foci has been extensively studied by Folkman's group [50]. These investigators have shown that, in the mouse model, the primary tumor inhibits the growth of distant metastases by secreting an angiogenesis inhibitor. Thus, if circulating unopposed estrogen is indeed associated with an increased risk of micrometastases, then extirpation of the primary tumor in such a setting may promote neovascularization and growth of those micrometastases by reducing the level of angiogenesis inhibitor and release of cytokines.

Conclusion

There is good evidence that surgery in the presence of circulating unopposed estrogen is

detrimental, as summarized in Table 1. Furthermore, retrospective studies suggest that the benefit of performing surgery during the luteal rather than the follicular phase of the menstrual cycle is comparable to that achieved following administration of systemic adjuvant therapy. Such a potentially large effect clearly merits further investigation. Randomized controlled trials addressing the effect of timing of surgery or neoadjuvant hormonal therapy on breast cancer mortality are urgently needed to confirm or refute the unopposed estrogen hypothesis. These trials may provide important insights into the natural history of breast cancer, and a basis for significantly reducing breast cancer mortality.

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