The Influence of Menstrual Cycle Phase on Surgical Treatment of Primary Breast Cancer: Have We Made Any Progress Over the Past 13 Years?

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The development and clinical course of breast cancer is modulated by a variety of endocrine influences. This observation led to the development of endocrine interventions, the first successful modality of targeted anticancer therapy. Today, it is widely recognized that endocrine interventions represent the most effective approaches to reducing the odds of recurrence and death for hormone-responsive primary breast cancer and for patients at risk for developing this disease (1–3). These accomplishments required the work of multiple laboratory-based and clinical investigators, the participation of tens of thousands of patients in prospective randomized trials, and the better part of the past three decades. During this time, a number of hypotheses were tested and, although several were proved with evidence, others were disproved, also with evidence.

In 1989, Hrushesky et al. (4) proposed that the timing of surgical interventions for breast cancer had substantial influence on the outcome of such interventions. Specifically, they proposed that premenopausal patients with breast cancer who were operated on during the perimenstrual period of the menstrual cycle had higher disease-free and overall survival rates than did patients who were operated on during other phases of the cycle. This conclusion was based on a retrospective analysis of 41 patients. Subsequently, a number of reports addressed this hypothesis, reports that eventually became part of a meta-analysis (5). The results of these studies were, at best, heterogeneous. Some (6,7) supported the hypothesis described by Hrushesky et al. (4), some (8,9) found no influence of the phase of the menstrual cycle on outcome, and one (10) found the opposite results: that patients who received their surgical therapy during the follicular phase did better that those who received their surgical therapy during the luteal phase.

Why such major differences in results? The most likely answer would point to differences in methodology. All studies designed to assess the efficacy of breast surgery in relation to the timing of the intervention during the menstrual cycle were retrospective. The phases of the menstrual cycle were determined arbitrarily on the basis of available information on the date of the last menstrual cycle before the surgical intervention. Even the definitions of follicular and luteal phases were made on the basis of different criteria in different institutions. Retrospective collection of data is fraught with inaccuracy, especially when the data being collected are not related to the primary objective of a clinical trial or research project. Furthermore, determining the timing of ovulation on the basis of the date of initiation of the previous menstrual cycle is notoriously inaccurate, as shown by a number of unwanted pregnancies resulting from avoiding intercourse during the periovulatory days as the major method of contraception. In fact, the follicular phase of the cycle is the less reliable or constant phase of the menstrual cycle, and assuming that ovulation will occur 15 days after the first day of menses often leads to major miscalculations. There are also statistical flaws when arbitrary definitions of the phases of the human menstrual cycle are adopted for analytical purposes. These have been eloquently reviewed by McGuire et al. (11) in an earlier issue of the Journal. Ten years ago, McGuire et al. (11) pointed to methodologic deficiencies of reports addressing the timing of breast surgical interventions during the menstrual cycle. Changing the definition of duration of a phase of the menstrual cycle by just a couple of days shifts substantial numbers of patients from the follicular to the luteal phase or vice versa. The only recognized and accurate method to identify the date of ovulation and therefore define the start and end of the follicular phase is by measuring plasma hormone levels. By such measurements, physicians would know whether the patient is in the follicular or the luteal phase of the menstrual cycle. Any other method leads to guessing—not a very reliable scientific method.

The article by Love et al. (12) in this issue of the Journal adds fuel to this fire. In their article (12), the authors describe the results of a retrospective, unplanned analysis to determine whether the timing of surgery during the menstrual cycle influences outcome. One of the strengths of their work is that the analysis is based on a prospective randomized trial and, therefore, the treatments administered were prospectively determined and controlled. In addition, estrogen receptor assays were performed on the tumors of many of the patients, which helped to identify the group of patients most likely to be affected by this hypothesis. The results are of interest because, on the one hand, they appear to refute the hypothesis proposed by Hrushesky et al. (4) 13 years ago. According to Love et al. (12), in premenopausal patients treated with mastectomy or lumpectomy, the timing of surgery in relation to the phases of the menstrual cycle had no effect on outcome. On the other hand, Love et al. (12) report a secondary, unexpected result of their analysis: that the timing of ovarian ablation and initiation of tamoxifen therapy in relation to the phase of the menstrual cycle appeared to have a substantial effect on outcome. Premenopausal patients who had their breast surgery and ovarian ablation during the luteal phase...
of the menstrual cycle had a better disease-free and overall survival rate than premenopausal patients who had their breast surgery and ovarian ablation during the proliferative phase of the menstrual cycle. On the basis of these data, one would have to think that if the timing of breast surgery had no impact on outcome, then it would be the timing of ovarian ablation and/or initiation of tamoxifen therapy that influenced outcome. There are a number of weaknesses in this observation. The basic one is that this is the result of an unplanned, retrospective subset analysis. Although some of the levels of clinical significance appear compelling, the methodologic pitfalls suggest that a healthy dose of skepticism is in order. For instance, the information about last menstrual period was considered “reliable” by the authors in only 79% of the patients enrolled in the original clinical trial. Furthermore, only two thirds of this subset had hormone receptor data and only half to two thirds of these had estrogen receptor-positive tumors. Now, despite reports to the contrary, there is no scientifically valid evidence that any endocrine intervention is effective for patients with estrogen receptor-negative tumors, as defined by a competent laboratory with good quality-control practices. Therefore, the question being asked by Love et al. (12) should really be restricted to the group of patients with reliable information about the phase of the menstrual cycle and estrogen receptor-positive tumors. With all the dropouts and exclusions, this subgroup represents between 25% and 28% of the original randomized group. The loss of two thirds to three fourths of the original population calls into question the reliability of any conclusions reached in this analysis. This reviewer would also question the accuracy and validity of the data about last menstrual period, because that observation was elicited initially only with the purpose of determining whether the patient was premenopausal. Because one period within the previous 12 months qualified the patient as premenopausal for purposes of this trial, further accuracy was presumably unnecessary at that time. To return to these data years later, with an entirely different objective that requires exquisite accuracy to classify the patient as to the timing of a specific intervention that occurred during a specific day may be asking more than the data can give. Using arbitrary definitions of proliferative phase (days 1–14 following the first day of the last cycle) and luteal phase (days 15–42 of the last cycle) adds this study to the host of previously published studies that did not include hormonal measurements. If the calculation of the phase of the cycle at the time of surgery is not completely reliable, then having a controlled therapeutic intervention is not very meaningful.

Another weakness of this study is that we are presented with multiple analyses. There is no mention of an adjustment in level of statistical significance to account for these many analyses. Thus, the old dictum, “If you torture the data enough, it will confess,” certainly applies.

So where do these results lead us? With all the shortcomings described, although the data certainly fail to support the hypothesis originally proposed by Hrushesky et al. (4), the data do not provide conclusive answers to the underlying controversy about the impact of the timing of breast surgery according to the phase of the menstrual cycle. As the authors themselves state, a prospective trial using state-of-the-art hormonal measurements and accurate determination of estrogen receptor status will need to be completed to answer this question. Such a trial will be difficult to perform because of the logistics of randomly assigning patients to wait for the selected phase of their menstrual cycle before surgical therapy is implemented. With the fear of the consequences of breast cancer ever present, patients want therapeutic interventions to start as soon as possible and do not want to wait for 2–4 weeks until the “right time” arrives.

However, the work by Love et al. (12) does raise a number of other interesting questions. Their principal conclusion seems to have shifted the focus of the controversy. It is not the timing of breast surgery that appears important but the timing of the endocrine intervention. The description of this part of the method is not detailed enough to determine whether this relates to the timing of ovarian ablation or to the timing of initiation of tamoxifen therapy. Perhaps the almost complete overlap between these two procedures in this study will preclude the identification of the most important intervention. Indirectly, these results also raise again the spectrum of the utility of an endocrine intervention in patients with estrogen receptor-negative tumors. It took the oncology community 20–25 years and tens of thousands of patients to refute the hypothesis that tamoxifen had clinically relevant antitumor properties in patients with estrogen receptor-negative tumors (13,14). There is no compelling biologic rationale to think that ovarian ablation will work in patients with estrogen receptor-negative tumors. Whether the observation of clinical effectiveness in the population described by Love et al. (12) is real or is the result of the same confounding variables (such as suboptimal estrogen receptor assessment) that extended the discussion in the evaluation of tamoxifen for 20 years will have to be considered very carefully before additional well-designed prospective trials are planned to try to confirm this hypothesis. Therefore, the only reliable method to confirm the hypothesis proposed by Hrushesky et al. (4) in 1989 or the one suggested by Love et al. (12) today is a prospective trial in which participants have careful hormonal measurements performed at baseline to determine their menopausal status and the phase of the menstrual cycle before any therapeutic intervention is instituted. Subsequently, randomized assignment to the definitive surgical intervention after stratification by phase of menstral cycle will eventually generate the needed evidence to support or reject this hypothesis. On the basis of existing evidence, there is no reason to time either breast surgery or ovarian ablation according to the phase of the menstrual cycle.

REFERENCES


(6) Badwe RA, Gregory WM, Chandy MA, Richards MA, Bentley AE, Rubens RD, et al. Timing of surgery during menstrual cycle and survival of


NOTE

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