The effect of timing of breast cancer surgery during the menstrual cycle phase on the axillary lymph node, estrogen receptor, progesterone receptor and c-erb B2

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Research

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Abstract

Background: Estrogen receptor (ER) and progesterone receptor (PR) positivity and c-erbB2 gene expression levels are important in determining breast cancer (BC) development and aggression. Although the importance of hormonal factors in tumor cell proliferation, migration and differentiation is increasing, it needs more evidence. The effect of BC surgery timing during the menstrual cycle on prognosis remains controversial. In order to clarify this hypothesis, we aimed to determine the importance of adjusting the timing of surgery according to the menstrual cycle by examining the relationship between ER, PR, c-erbB2 gene and the menstrual cycle phase in patients with premenopausal BC.

Method: Our study was designed retrospectively. 50 patients with premenopausal BC who were operated were included in the study.

Results: Our results showed that the patients in the luteal phase had higher ER positivity, PR positivity and c-erbB2 negativity, and the number of metastatic axillary lymph nodes was lower than the patients in follicular phase.

Conclusion: BC surgery during the luteal phase in pre-menopausal women is associated with a better clinical outcome. Although larger-scale studies are needed, our results suggest that better results can be achieved by performing surgery in luteal phase in BC patients during premenopausal period.

Introduction

Breast cancer (BC) is the most common malignancy and the leading cause of cancer related death among women all around the world [1]. Although developed countries report higher rates of BC incidence and mortality, changes in the incidence of BC are most dramatic in low-middle income countries (LMC) including Turkey [2]. The World Health Organization (WHO) categorized countries into four categories: basic, limited, developed and maximum. Turkey is a middle income country between limited and enhanced level regarding their sources [3, 4]. Age and induced abortion were found to be significantly associated with increased BC risk whereas oral contraceptive use was observed to be associated with decreased BC risk among Turkish women in Istanbul [2].

BC care is complex and requires a multidisciplinary approach. There is mounting evidence that the timing of surgery within the menstrual cycle has a significant effect on prognosis in premenopausal women with breast carcinoma [5-12]. For the first time in 1991, the effect of the timing of surgery in patients with both estrogen receptor (ER) positive and negative tumors was demonstrated by Badwe et al. [5]. Timing of operation in relation to menstrual phase might affect outlook in premenopausal women with operable breast cancer.

In the light of the data in the literature, it was aimed to investigate the importance of adjusting the timing of surgery according to the menstrual cycle by examining the relationship between prognostic factors as
axillary lymph node, ER, progesterone receptor (PR), human epidermal growth factor receptor-2 (HER-2/neu or c-erbB2) gene and the menstrual cycle phase in patients with premenopausal BC.

**Methods**

**Study design and participants**

Approval from the Ethics Committee of Cerrahpasa Medical Faculty for this study was received, and the study was conducted in conformity with the Declaration of Helsinki. Written informed consent of all participants was obtained before starting the study (No: 22721 date: 8 February 2019). This retrospective study was conducted in Cerrahpasa Medical Faculty in period from March to October 2019. The study included 50 patients with premenopausal BC who were followed up in the Department of Oncology, Cerrahpasa Medical Faculty, and Istanbul University-Cerrahpasa. Clinical findings, menstrual cycle phase, number of axillary lymph nodes, estrogen receptor and c-erbB-2 gene expression results, treatment and clinical course of the patients were retrospectively obtained from the polyclinic file of the patients. Postmenopausal breast cancer patients were not included in the study. Last menstrual period was also categorised according to the menstrual cycle phase definitions of Badwe et al (1991) (luteal: days 0–2 and 13–32; follicular: days 3–12) [5].

Pathology investigations include evaluation of primary tumor and lymph nodes. ER, PR and HER-2/neu status were evaluated by immunohistochemistry (IHC) and silver in situ hybridization (SISH). ER, PR and HER-2/neu status were documented in the patient files.

**Statistical Analysis**

In this study, SPSS 21.0 program was used as statistical method. Descriptive data for continuous variables are presented as mean ± standard deviation (SD). Categorical variables are given as frequency and percentage.

**Results**

Table 1 displays baseline characteristics for patients with premenopausal breast cancer. At the time of the surgical procedure, 23 women (46%) were classified as luteal phase; and 27 women (54%) were classified as follicular phase. No significant difference was found between the mean age of the patients in the luteal phase and follicular phase. The number of metastatic axillary lymph nodes in the luteal phase was significantly lower in women with breast cancer than in the follicular phase. In 8 patients in the luteal phase (34.78%), the tumor was localized in the left breast and in the right breast in 15 patients (65.22%). In 12 patients in the follicular phase (44.44%), the tumor was localized in the left breast and in the right breast in 15 patients (55.56%). ER positivity, PR positivity and c-erb B2 negativity were higher in the luteal phase than follicular phase.
|                                | Luteal phase (n = 23) | Folicular phase (n = 27) | p   |
|--------------------------------|-----------------------|--------------------------|-----|
| Age                            | 40.00 ± 5.52          | 40.44 ± 5.14             | 0.770 |
| Metastatic axillary lymph nodes | 1.30 ± 2.46           | 3.37 ± 3.62              | < 0.001 |
| Breast cancer location         | 8 (%34.78)            | 12 (%44.44)              | 0.343 |
| Left                           | 15 (%65.22)           | 15 (%55.56)              |     |
| Right                          |                       |                          |     |
| ER status                      | 0(%0) / 11(%48) / 3(%13) / 9(%39) | 11 (%41) / 12(%44) / 4(%15) / 0(%0) | < 0.001 |
| PR status                      | 4 (%17) / 6 (%26) / 6(%26) / 7(%30) | 15 (%56) /10(%37) / 2(%7) / 0(%0) | < 0.001 |
| c-erbB-2 status                | 20 (%87) / 3(%13) / 0(%0) / 0 (%0) | 12(%44) / 3(%11) / 1(%4) / 11(%41) | < 0.001 |

**Discussion**

The findings from both qualitative and quantitative analysis of studies on performing BC surgery in a certain phase of the menstrual cycle are unclear. In the good phase of the menstrual cycle (Days 0 – 2 and 13–32), women with ER (+) tumors have a significantly better outcome than those with ER (-) tumors and follicular phase surgery is associated with a poor prognosis regardless of hormone status [11].

The current study was set to investigate the importance of adjusting the timing of surgery whether the effect of menstrual cycle phase on the axillary lymph node, ER, PR and c-erbB-2 gene in patients with premenopausal breast tumors. The number of metastatic axillary lymph nodes in the luteal phase was significantly lower in women with BC than in the follicular phase.

A specific breast phenotype with lack of ER, PR, and c-erbB-2 expression, the so-called “triple-negative” phenotype, is linked with poor prognosis [13]. In the light of the data in the literature, this study was set to investigate whether the effect of menstrual cycle phase on the axillary lymph node, ER, PR and c-erbB-2 gene in patients with premenopausal breast tumors. It is concluded that prognostic factors are better in patients with luteal phase. In this way, we believe that luteal phase can be used to determine the
operation time for women in premenopausal period. With the mentioned study is a study feature will be the first time in Turkey.

The development and clinical course of BC is modulated by various endocrine effects. It is now widely recognized that endocrine interventions represent the most effective approaches for reducing the risk of recurrence and death for hormone-responsive primary breast cancer and reducing patients at risk of developing this disease. In the last 30 years, some hypotheses have been established on the basis of the endocrine-cancer relationship, and although many have been proven, there are still hypotheses awaiting clarification.

There is still discordance between studies and well-conducted prospective studies have provided evidence, both for and against, rescheduling surgery to the luteal phase [14]. Our study demonstrates that, the number of metastatic axillary lymph nodes in the luteal phase was significantly lower in women with BC than in the follicular phase. ER positivity, PR positivity and c-erb B2 negativity were higher in the luteal phase than follicular phase. These results show that prognostic criteria are well observed in luteal phase. One of these hypotheses was proposed by Hrushesky et al. [15] in 1989 and they suggested the concept of surgical intervention to treat BC in premenopausal women according to the stage of the menstrual cycle. The authors suggested that premenopausal patients with BC who were operated during the perimenstrual period of the menstrual cycle had higher disease-free and overall survival rates compared to patients operated in other phases of the cycle [5]. However, according to the results of the retrospective, prospective and meta-analysis studies performed on this hypothesis for the last three decades; while some studies [5, 16] support Hrushesky et al. [15], there are studies reporting that the menstrual cycle does not affect the outcome [17, 18], or that the opposite results (patients who underwent surgical treatment in the follicular phase are better than those receiving luteal phase surgery) [19].

Continuous fluctuations of estrogen and progesterone throughout the reproductive period in women affect the phenotype and function of breast, stromal and immune cells including macrophages and regulatory T cells, as well as the turnover of the mammary epithelium, stem cells, and extracellular matrix. Collectively, these events can lead to genome instability, increase the likelihood of random genetic mutations, reduce immune supervision and increase tolerance in the mammary gland; thus increasing the risk of breast cancer onset [20]. In addition, fluctuations in estrogen and progesterone throughout the menstrual cycle direct the proliferation, differentiation and apoptosis in the mammary gland epithelium [21]. Menstrual cycle phases in women; Pituitary gland hormones, follicle stimulating hormone and luteinizing hormone and ovarian hormones are regulated by fluctuations in estrogen and progesterone. Estrogen exerts proliferative effects on mammary epithelial channels by direct ERs, as well as up-regulates the expression of PR during the luteal phase of the cycle [20]. ER, PR and c-ERBB2 (HER-2/neu) are important therapeutic and prognostic markers for breast carcinoma [22]. Vasei et al. [23] showed that the ER and PR are higher in the luteal phase. In another study, they reported that ER positivity was higher in the follicular phase and the PR was found to be independent of the menstrual cycle; and if the condition of the hormone receptor is found to be negative, it is necessary to reevaluate the phase of the
menstrual cycle in which the operation is performed [24]. Liu et al. [25] reported that surgery performed during the follicular phase provides a more favorable prognosis compared with the luteal phase.

Our study suggests that BC surgery during the luteal phase in pre-menopausal women is associated with a better clinical outcome. Although larger-scale studies are needed, our results suggest that better results can be achieved by performing surgery in luteal phase in BC patients during premenopausal period. Prospective randomized clinical trials are also necessary to determine the full extent of survival benefits of luteal surgical timing.

**Declarations**

**Availability of data and materials**

The raw data of this paper are available upon reasonable request to the corresponding author.

**Ethics approval and consent to participate**

The study was approved by the Hospital Ethics Committee (No: 22721 date: February 8 2019).

**Consent for publication**

Not applicable

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

Not applicable

**Authors’ contributions**

**BPK and HU**: design, contributed to writing the manuscript and coordination. **BPK, MV and CP**: data collection, contributed to writing the manuscript. **SD and RG**: data analysis, contributed to writing the manuscript. All authors read, commented, and approved the final manuscript.

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