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Prognostic effect of menstrual cycle on timing of surgery in premenopausal breast cancer patients

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Abstract

BACKGROUND: It is controversial whether surgery during different menstrual phases (a kind of host milieu may influence biological characteristics of micrometastatic foci) affects clinical outcomes.

METHODS: Survival outcomes were compared between patients who underwent surgery during the follicular (cycle days 1 to 14) and luteal (days 15 to 31) phases. A range of cutoff days from day 10 to 22 was used to observe the risk trend.

RESULTS: The follicular phase was associated with a more favorable prognosis than the luteal phase in disease-free survival (DFS) [hazard ratio (HR) .318, 95% confidence interval (CI) .10 to .99, $P = .049$] and overall survival (OS) (HR .260, 95% CI .07 to .92, $P = .036$). Similar results were detected when the cutoff day was set at days 14, 18, and 19 in DFS and days 11, 13, and 14 in OS. A low HR flat fluctuation was observed from cutoff days 10 to 22, and the risk went up thereafter for both DFS and OS.

CONCLUSION: Surgery performed during the follicular phase provides a more favorable prognosis compared with the luteal phase.

Over decades, studies on clinical outcomes in breast cancer have thrived with the development of therapeutic approaches. Current studies mostly focus attention on tumor cells rather than microenvironments. As proposed in the "seed and soil" hypothesis, specific organ microenvironments (the "soil") provides for selected cancer cells (the "seeds") arising from primary tumors.[1] Tumor recurrence and metastasis is the consequence of dynamic cross-talk between tumor cells and microenvironments. Clinical research has found that the host milieu caused by surgery may affect clinical outcomes, such as postoperative fever and flap necrosis.[2,3] All these phenomena indicate that host milieu during the perioperative period may influence biological characteristics of micrometastatic foci and promote cancer migration, growth, and recurrence.

It has been recognized that the action of sex hormones is closely associated with the development of breast cancer. The levels of female hormones rise and fall during a normal female's menstrual cycle. Estrogen rises throughout the first

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half of the menstrual cycle, then falls, and rises and falls again during the second half of the cycle. Progesterone remains low in the first half of the cycle and rises in the second half. The menstrual cycle ranges between 15 to 45 days, averaging at 28 days with a standard deviation of 3.95 days.[4] The mean lengths of the follicular and luteal phase are 14.37 and 14.26 days, respectively, with tolerance limits of 11 to 17 days for each phase.[5] The 2 menstrual phases might provide distinct host milieu even in the same woman. It is contentious nowadays whether breast surgery during certain menstrual phases could stimulate the growth of micrometastases and facilitate the development of macrometastases and recurrence, and whether surgery during a certain phase would provide patients with a favorable survival.

Theoretically, under a combined action of a high level of estrogen and progesterone, host stress to surgery and increased tumor cells in the bloodstream postoperatively, surgery during the luteal phase may promote the formation and proliferation of micrometastases, which would in turn lead to recurrence. On this premise, we carried out a retrospective study to determine whether timing of surgery during different menstrual cycle phases was associated with prognosis in premenopausal breast cancer.

Patients and Methods

Patients

We retrospectively analyzed a database of patients who underwent breast surgery at the Fudan University Shanghai Cancer Center between 2000 and 2002. Designating the first day of menstruation as day 1, we enrolled premenopausal women with regular menstrual cycles. Surgical treatment consisted of a biopsy followed by a mastectomy or breast-conserving surgery with or without sentinel node biopsy and/or axillary nodal dissection. Chemotherapy and/or radiotherapy and/or endocrine therapy were administered in accordance with international treatment guidelines. We applied the 14th cycle day as the cutoff day to discriminate the follicular from luteal phases. The menstrual cycle was divided into the follicular phase (cycle days 1 to 14) and the luteal phase (days 15 to 31). Patients with irregular menstrual period or age greater than or equal to 60 were excluded. All patients were followed up every 3 to 6 months for the next 7 to 9 years for disease recurrence, metastasis, second primary tumors, and death. Recurrence was diagnosed by biopsy, or by scan of bone, chest, abdomen, pelvis, or skull. Whenever the tumor recurred, additional information, such as sites of recurrence and therapy, was requested.

Immunohistochemistry

For each patient in our study, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) were determined by immunohistochemical staining, which was carried out under a standard operating procedure in the pathology department of Fudan University Shanghai Cancer Center. All primary monoclonal antibodies were from Dako, Inc. At least 2 pathologists assessed the percentage and the intensity of stained tumor cells, denoted respectively as the proportion score and the intensity score. The former was interpreted as follows: 0 required no staining, 1 required less than or equal to 25% of cells stained, 2 required 25% to 50% of positive cells, 3 required 50% to 75% of positive cells, and 4 required greater than 75% of staining. As to the intensity score, a negative result was defined as 0, weakly positive as 1, moderately positive as 2, and strongly positive as 3. The final score was calculated as the product of the proportion and intensity scores. Thereby, staining results ranged between a score of 0 to 12. The scoring system for ER and PR was defined as negative for score 0 and positive for scores of 1 to 12 with staining of carcinoma cells, whereas HER2 was defined as negative for scores of 0 to 8 (namely, 0, 1+, and 2+ in the DAKO scoring system) and positive for strong membranous staining with scores of 9 to 12 (namely DAKO score 3+).

Statistical analysis

Disease-free survival (DFS) was defined as the time from surgery to the earliest recurrence of tumor at any local, regional, or distant location; detection of a second primary cancer; or death as a result of any cause without recurrence. Overall survival (OS) was defined as the time from primary treatment to death as a result of any cause. Clinicopathologic parameters were compared between different subgroups using the Student t test for continuous variables and the chi-square test for categorical variables.

Survival distributions were performed by the Kaplan–Meier method and were compared using the log-rank test. Multivariate Cox proportional hazards regression analysis was applied to modeling the relationship between timing of surgery and survival outcomes, adjusted for age ($\leq$3 years, $>$35 years), lymph nodes (0, 1 to 3, 4 to 9, $\geq$10), tumor size ($\leq$2, 2 to 5, $>$5 cm), and ER/PR (negative, positive) and HER2 status (negative, positive). Interaction between ER/PR status and the menstrual cycle phase at surgery was assessed. Hazard ratio (HRs) were presented with 95% confidence intervals (CIs). All statistical tests were 2 sided and the difference was defined as significant at a P value of less than .05. All statistical analyses were performed with the Stata statistical software package (version 10.0; Stata Corporation, College Station, TX).

Results

General characteristics

A total of 554 premenopausal patients with a median age of 44 (range 25 to 57) years were included in the study.