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PROGNOSIS OF PATIENTS WITH BREAST CANCER RELATED TO THE TIMING OF OPERATION DURING MENSTRUAL CYCLE

Zhang Baoning 张保宁

Department of Surgical Oncology, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021

Objective: To evaluate the effect of operation timing during menstrual cycle on the prognosis of patients with breast cancer. Methods: 218 operated premenopausal patients with breast cancer had been followed-up for more than 10 years. Prognostic factors related to these patients had been selected to be underwent univariate analysis and multivariate analysis by Cox regression model. Results: Univariage analysis showed that the menstrual timing of operation, as other Known prognostic factors (tumor size, node status, histological grade, TNM classification, adjuvent systemic therapy, etc), had an influence on the patients' outcome. Multivariate analysis by Cox regression model indicated that disease-free rate and overall survival rate of patients operated during the periovulatory phase (123 cases) were significantly superior to those operated during the premenstrual phase (95 cases) ($P<0.01$). There were no significant differences in prognosis between patients who received operations during the follicular phase (96 cases) and those during the luteal phase (122 cases) ($P>0.01$). Conclusion: Probably there is an optimal timing of operation for premenopausal breast cancer patients. Any prospective, randomized clinical study should be carried out to make this problem clear.

Key words: Breast cancer operation, Menstrual cycle, Prognosis

In the recent years, clinicians and oncologists have found, by Cox regression model multivariate analysis, that the prognostic factors of breast cancer are: age, size of the primary lesion, lymphatic metastasis, TNM stage, pathological type, estrogen receptor, cellular multiplication rate and its DNA content. All these prognostic factors exist intrinsically when the patient visits the doctor and, hence, is unchangeable. Timing of the operation, if ever proved as another prognostic factor, will be at the hands of the surgeons to steer the patient's course. Trying to solve this problem, we have accomplished a retrospective analysis of 218 premenopausal breast cancer patients, surgically treated between March 1958 and December 1984. The purpose of this study is to assess the impact of operation timing on the prognosis.

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MATERIALS AND METHODS

Criteria of Entry of Patients

From March 1958 to December 1984, a total of 4147 breast cancer patients was admitted to our hospital for treatment. Patients who conformed to the following criteria were entered into the present study:

Inpatients of our hospital for the first surgical treatment;

Premenopausal patients with regular menstruation and accurate data about last menstrual period (LMP);

No treatments directly against the ovary before, e.g. ovarian ablation or irradiation;

Having been followed-up for more than ten years.

General Clinical Data:

Of the 218 patients, the ages ranged from 21 to 50 years, with an average of 40. Side of lesion: right/left=109/109; TNM stage: I 29, IIa 68, IIb 77, IIIa 36, IIIb 4 and IV 4; T stage of the primary lesion: T1 41, T2 124, T3 48 T4 5; N status: (+) 120, (-) 98; pathological type: intraductal carcinoma (non-infiltrating) 4, lobular carcinoma (early infiltrating) 1, infiltrating carcinoma simplex 96, infiltrating ductal carcinoma 46, schirrous carcinoma 29, mucinous adenocarcinoma 21, medullary carcinoma 20 and squamous cell carcinoma 1; Type of operation: radical mastectomy 185, extended radical mastectomy 21, simple mastectomy 10 and segmental resection of the breast 2. Twenty-three patients received preoperative treatments, e.g. radiotherapy, chemotherapy or Chinese medicine herbs. 163 patients received postoperative treatments like above.

The Mentioned Clinicopathologic Factors and Treatment Types were Stratified as Follows for Statistical Analysis

The patients' age: 21—29, 30—39, 40—50 years old. Side: left, right. Size of the primary lesion: T1<2cm, T2 2—5cm, T3>5cm, T4 invasion of chest wall or skin. Lymphatic metastasis: L(-), L(+). TNM stage: I, IIa, IIb, IIIa, IIIb, IV. Pathological type: carcinoma simplex, schirrous carcinoma, mucinous adenocarcinoma, medullary carcinoma and other types. Preoperative treatments: treated, untreated. Timing of operation in menstrual cycle: premenstrual phase and periovulatory phase, follicular phase and luteal phase. Type of operation: extended radical mastectomy, radical mastectomy, simple mastectomy and segmental resection. Postoperative treatments: radiotherapy, chemotherapy, chemotherapy plus radiotherapy, untreated.

The timing of operation within the menstrual cycle was defined as follows:

1. Premenstrual phase and periovulatory phase—
   premenstrual phase: days 0-6 and 21-40 LMP 95 patients
   periovulatory phase: days 7-20 LMP 123 patients
2. Follicular phase and luteal phase—
   follicular phase: days 4-14 LMP 96 patients
   luteal phase: days 15-40 LMP 122 patients

Statistical Analysis

All the data of clinical condition were processed by the software designed by Liu. First, the ten characteristic factors: age, side size of the primary lesion, lymphatic metastasis, TNM stage, pathological type, timing of operation in the menstrual cycle, type of operation, pre- and post-operative treatment, of these 218 premenopuasal breast cancer patients were analyzed by the univariate method. Then, multivariate analysis by Cox regression model was done to assess the prognostic significance of operation timing as in the periovulatory phase and the premenstrual phase.

RESULTS

Univariate Analysis

By univariate analysis, we found that, in premenstrual breast cancer patients, timing of operation during the menstrual cycle was prognostic in addition to: size of the primary lesion, lymphatic metastasis, TNM stage, pathological type, post-operative treatment (Table 1). The 5-, 10-, 15-year survival rates of 123 patients were operated upon during the periovulatory phase were 82.9%, 78.86% and 75.63% respectively. Those of 95 patients were operated upon in the premenstrual phase were 68.42%, 57.89% and 52.63%. It is obvious that the results of the former periovulatory subset are better than those of the latter premenstrual subset (Figure 1) ($P<0.05$). The disease-free survival rates are also significantly superior in the former ($P<0.05$). The Cohort analysis with the patient-year as the divider is shown in Table 2. Stratification of TNM stage shows that the prognosis of Stage IIa and IIb lesions operated upon in the premenstrual phase while Stage I and IIIa groups do not show any significant difference. The demonstration of a survival difference in the follicular and luteal phases is unsuccessful ($v=1$, $\chi^2=2.11$, $0.1<P<0.2$).

Multivariate Analysis by Cox Regression Model

Multivariate analysis of the prognostic value of

Table 1. Result of univariate analysis of 218 breast cancer patients

Sequence	Characteristics factors	Freedom	Chi^2	*P*
1	age	2	1.6	>0.3
2	side of lesion	2	1.5	>0.3
3	size of lesion	3	10.93	<0.02
4	lymphatic metastasis	1	16.59	<0.001
5	TNM stage	4	21.83	<0.001
6	pathologic type	4	10.98	<0.05
7	timing in menstrual cycle			
	1. premenstrual & periovulatory p phase	1	3.85	<0.05
	2. follicular phase & luteal phase	1	2.11	>0.1
8	preoperative treatment	1	0.36	>0.5
9	type of operation	2	4.4	>0.1
10	postoperative treatment	3	17.39	<0.01

timing of operation in the periovulatory phase by Cox regression model shows that, with the influence of TNM stage adjusted, the relative risk of the periovulatory operation group $RR=exp^{[\beta]}=e^{0.71}$) and that of the premenstrual operation group RR=16.44 ($RR=exp^{[\beta]}=e^{2.8}$), which is eight times larger than the former. There is a very conspicuous significance between the two groups ($P<0.01$). After the adjustment of the lymphatic metastasis by Cox regression model, there still exists an obvious significance ($P<0.005$).

DISCUSSION

Review on the Timing of Operation for Breast Cancer

In 1836, Sir Astley Paston Copper observed in his 'Practice and Principles of Surgery' that advanced breast cancer regularly waxes and wanes during the patient's menstrual cycle. In 1896, GT Beatson in the Lancet demonstrated that advanced breast cancer can resolve following oophorectomy of the premenopausal

Table 2. Comparison of mortality rates person-year as denominator between periovulatory and premenstrual groups

No. of year	Numerator denominator	Perivulatory group (n=123)	Mortality rate (%)	Premenstrual group (n=95)	Mortality rate (%)	Total
Y<5	No. died	21	3.73	30	7.64	51
	person-years	563.55		392.55		955.9
5≤Y<10	No. died	5	1.04	10	3.52	15
	person-years	479.75		284		764.15
10≤Y15	No. died	4	1.50	5	2.66	9
	person-years	266.55		187.9		454.45
15≤Y	No. died	1	0.37	0	0.00	1
	person-years	270.4		192.75		463.15
Total	No. died	31	1.96	45	4.26	76
	person-years	1580.25		1057.4		2637.65

unadjusted analysis: RR=2.15 (95% lower limit 1.36, upper limit 3.13), AR=31.66

patient. In 1952 and 1953, Huggins and Luft, respectively, demonstrated tumor resolution following adrenal and hypophyseal resection in women with advanced breast cancer. In the 1960's, Elwood Jensen initiated our growing understanding of the molecular basis of these intricate connections between host and cancer.[4] Ratajczak and his associates in 1988[5] reported, on animal experimental work, that they chose to operate on female mice model implanted breast cancer when the animals were in estrous, i.e., during ovulation. They found that the incidence of pulmonary metastasis was conspicuously reduced which aroused extensive attention in the clinicians. This finding was proved to be true in clinical practice in 1989. Hrushekey, et al.[6] reported on 41 cases of breast cancer, nineteen of these 41 patients were operated on in the periovulatory phase (days 7-20 LMP) and 22 in the premenstrual phase (days 0-6, 21-36 LMP).

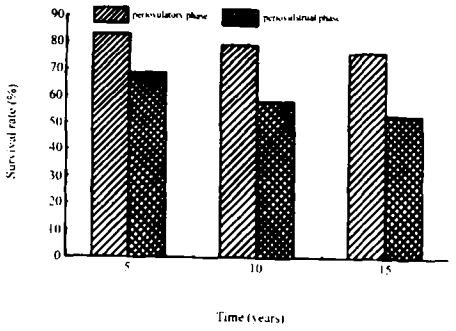

Fig. 1. Survival of breast cancer patients on whom operation was performed in the periovulatory phase vs. premenstrual phase.

Comparison of the results showed that the recurrence rate and mortality rate in the premenstrual group were 4 times as high as the periovulatory group. He believed that there was a safety timing for operation in the premenopausal patients suffering from early breast cancer. The eight subsequent retrospective studies, summarizing 1213 premenopausal patients, all arrived at the same conclusion as Hrushesky and his associates did. These data were presented at international conferences later.[4] Yet, some other scholars had arrived at different conclusions.[7-9] Donegan, et al.[8] reported that, on 55 patients were operated on in the premenstrual phase and 42 patients in periovulatory phase, he had not observed any difference in the respective survivals nor in the time of biopsy. He advocated that there should be any time suitable for operation of premenopausal breast cancer patients. Other authors,[10-12] defining the menstrual phase differently, found that days 3-12 and days 0-2, 13-32 groups gave very different survivals. Badewe and his associates,[10] grouping his patients as 3-12, 0-2 and 13-32, found, by multivariate analysis, that the timing of operation was as important as the presence of lymphatic metastasis and was closely related to the presence of pathologically positive lymph node metastasis. This relationship was especially pronounced in T1 patients. There are, however, other authors maintaining the opposite views, like Powles[13] and Corder[14] who did the grouping identically and concluded that similar survival rates of two groups were obtained. There are also other authors[15,16] who found that patients were operated on during days 1-12 LMP (follicular phase) gave poorer survivals than those operated after days 13 (luteal phase). Senie, et al.[17] reported that patients were operated on in the first half phase of the menstrual cycle (days 1-14 LMP) gave a 14% higher recurrence rate than the other patients were operated on in the second period. In short, there are still in controversy in this issue. At the present time, three questions remain to be answered: 1. Is there an optimal timing to perform the operation on a premenstrual breast cancer patient? 2. If so, what is the biological basis of such optimal timing? And 3. Are the data presently available enough to enable us to set a timetable for surgery in the premenopausal breast cancer patient?

Is There A Salutary Phase for Operation on Premenopausal Breast Cancer Patients?

Our data show that there is an obvious superiority in the periovulatory group to that in the premenstrual group ($P<0.05$). After stratification, timing of operation is found to be closely related to the prognosis in state II breast cancer. Due to the limited number of cases, stage I and IIIa patients did not show any significance. What stage IIIb and IV patients need is combination therapy with surgery as supplement. Also due to the limited number of cases in periods (in the periovulatory or the premenstrual phase). Our conclusion, conforming with some of the reported materials,[4,6] support the belief of presence of a salutary phase for operation. We think the method of retrospective study discloses an intrinsic grave defect even though there have been some improvements in the present clinical case analysis, i.e., this study is not a randomized investigation. With a unrandomized entry, the choice of treatment is inevitably inclined which is apt to lead to a false positive conclusion. Another drawback in our study is the small size of the samples. The choice of sample needs an accurate record of LMP and a long follow-up, both of which greatly influenced the number of case entry to a total of merely 218. Further stratification of these samples gives 29 stage I cases that are too small to give an allowable error of sampling. This, in turn, causes inaccuracy in the final conclusion. Too large an error in sampling would easily lead to a false negative conclusion. In the recent reports, this non-uniformity has led to opposite conclusions even on the same operation timing. Therefore, all we could say to the question whether there is an optimal timing of operation for premenopausal breast cancer patients is -

possibly! And we say it with absolute lack of resolution. As being well known, the body's NK cells which, in turn, would lead to different degrees of metastasis and cancer cell implantation. Therefore, different timing of operation would possibly lead to varying prognosis.

This operation timing has been adopted in some hospital but most surgeons are still waiting for more convincing proof for further action.[19] We believe that while proceeding with the bio-characteristic studies of breast cancer, we should carry out an extensive, cooperative, prospective and randomized trial to arrive at a final answer to the question whether there is an optimal timing of operation for premenopausal breast cancer patients, how much influence it has, and how to intervene in the balance between the estrogens and luteal hormones by pharmacology. This is how we could improve the result of treating breast cancer efficiently.

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