

ANALYSIS ON THE RELATIONSHIP OF DIFFERENT TREATMENT STRATEGIES AND PROGNOSIS OF 1636 PATIENTS WITH BREAST CANCER

GUIZHI DONG, HONG CHAO MU*, DEGUANG WANG
The People's Liberation Army 404th Hospital 264200, China

ABSTRACT

Objective: Through analysis of relationship of a large sample of breast cancer tumors and prognosis factors we tried to establish a clinical practical prognostic model, so as to provide the scientific basis for preventing & treating breast cancer.

Materials and methods: From January 2005 to December 2009, 1636 cases of patients with breast cancer were enrolled in this study. Retrospective analysis and comparison on related influence of treatment strategies on survival prognosis was performed through analysis of medical records and follow-up.

Results: In follow-up of 1636 breast cancer patients, 154 cases lost, follow-up rate was 90.6%, i.e. 1482 cases were effective. Treatment related factors, including surgery, chemotherapy, radiation therapy, were related to breast cancer patients long-term survival, ($P < 0.05$).

Conclusion: Treatment related strategies are independent prognostic factors influencing long-term survival of breast cancer patients.

Key words: Breast cancer, Prognosis, Follow-up, Treatment strategies.

DOI:10.19193/0393-6384_2016_1_16

Received May 30, 2015; Accepted November 02, 2015

Introduction

Breast cancer has become one of the most common malignant tumors of women in the world. In most large and medium-size cities of China, it has occupied the first position of female cancer mortality and has increasingly become an important factor influencing female's physical and mental health, family happiness and the social stability. As breast cancer morbidity rises, it becomes more and more important to take a retrospective analysis of the data of diagnosis and treatment of the disease⁽¹⁾. It will significantly enhance the survival rate of patients by making accurate judgment of the prognosis of patients as well as creating a sensible, effective and individualized plan.

This article tries to analyze the relationship of different treatment strategies and prognosis thor-

ough making a data summary of 1636 people with breast cancer between January 2005 and December 2009 in Weihai, which has profound guiding implications for the later treatment and aims to provide scientific foundations for clinical prognosis analysis.

Materials and methods Clinical Data

1636 clinical cases including the ones which have clear histology and clinical stages are selected from the three representative municipal hospitals of Weihai (PLA 404 Hospital, Weihai Municipal General Hospital and its southern branch, Weihai Women and Children's Hospital) from January 2005 to December 2009. According to the analysis purpose, unified questionnaires were designed in reference to some relevant data. Through the questionnaires, different treatment methods, for exam-

ple, surgery, chemotherapy regimen and cycle, radiation therapy are collected (the chemotherapy regions of the initial treatment are chest wall, axillary fossa and collarbone, excluding the parts of the chemotherapy after metastasis) All patients get confirmed diagnoses by biopsy or surgical treatment. Patients with hematogenous ($p < 0.05$) metastatic tumors are ascertained by clinical check including CT, MRI, type-B ultrasonic and Bone Scintigraphy. The clinical data look-up continued and finalized by December 2010.

When a same name was repeatedly found in the chosen hospitals during the data collection, then a check-up of these patients' s age of onset, home address, telephone number, contacts and other relevant information is taken, the data will be consolidated if the most information of these patients are consistent. The patients who suffer from breast cancer before December, 2004 while still receive treatment are involved in the analysis too. Some variables may change because this is a retrospective analysis; therefore, some variables have been defined. For instance, the age of onset and clinical stage are subject to case records of the first diagnosis. The treatments conditions are subject to case records. Other available data were adopted if some data were not complete. The features of different variables and their assignments in the stratification of the statistical software SPSS13.0 are shown in the table 1.

Variable assignment	and n	survival rate (%)				median survival time (month)	P-valued between groups
		1-year	3-year	5-year	10-year		
surgery methods						115.79	0.0004
un-operated (0)	16	80.77	65.38	65.38		108+	
modified radical mastectomy (1)	782	95.12	88.58	80.11	53.18	148.84	
breast conserving surgery (2)	116	99.14	97.02	91.31	91.31	180+	0.0256
chemotherapy regimens						9.252	
anthracycline-based and free-taxane (1)	331	96.86	92.59	83.22	70.50	240+	
taxane-based and free-anthracycline (2)	34	95.92	95.92	95.92	67.96	107.49	
anthracycline combine with taxane (3)	253	95.76	87.97	84.63	78.58	240+	
the rest (4)	89	90.56	82.70	68.69	55.60	146.42	0.0472
radiation therapy						10.67	
free-radiotherapy(1)	374	94.33	85.24	80.68	55.82	189.38	
intraoperative radiotherapy (2)	356	96.19	91.14	81.75	58.34	149.14	

Table 1: the relationship of different treatment strategies and prognosis of the 1636 patients.

Follow-up

In addition to cases check-up, the data is also collected through phone call follow-up, interview and household survey with aid of police.

Statistics analysis

The statistical software SPSS13.0 was used to perform statistical analysis. The variables were filtered based on the standard "a=0.05". The survival curve was drawn by life-tables, the comparison of survival rates are checked by χ^2 . The three variables will be input into computer after having been quantitatively assigned. The statistics analysis including Cox-model single factor and multi-factor analysis, the Cox model adopted forward stepwise method to analysis the statistics so as to judge the risk factors of prognosis. The variables are put into the model in the form of disulfoxide variables as considering some variables may not have hierarchic relationship when they are at different levels. The study endpoints of patients' 5- and 10-year survival rate are established according to the time when the cases are included in the analysis. The prognostic factors, which affect patients' 5- and 10-year survival rate, were analyzed and compared retrospectively.

Results

Follow-up results

1636 breast cancer cases have been collected and analyzed by December of 2010, the deadline of follow-up is on April, 15th, 2011. In follow-up of 1636 breast cancer patients, 154 cases lost, follow-up rate was 90.6%, i.e. 1482 cases are effective. The lost and the patients who still alive till the deadline of follow-up are defined as "censored data" and "truncated data" respectively in this analysis. The survival time which starts from diagnosis time to death time is counted by month, however, it should be counted by 10-year way if the survival over 10 years. There are 1270 patients still alive and 212 dead by the end of follow-up.

Survival data of patients

The 1-, 3-, 5- and 10-year survival of 1482 patients are 94.91%, 88.64%, 80.64%, 56.17% respectively and the median survival time is 154.87 months. The Cox single factor analysis of the relationship of relevant treatment factors and prognosis of 1636 patients is shown in table 1.

Among the relevant factors of treatment and prognosis, the surgery methods, chemo-therapy, radiation therapy all are significantly correlate with long term survival rate. The patients who choose different surgery methods including breast conserv-

ing surgery, modified radical mastectomy and un-operated are significantly correlate with long term survival rate, $X^2=115.794$, $P=0.004$. Both 5- and 10-year survival rates of the patients who accept breast conserving surgery are 91.93%, which are higher than the ones who take modified radical mastectomy (The survival rates are 80.11% and 53.18% respectively). None of the un-operated survives over 10 years (figure 1).

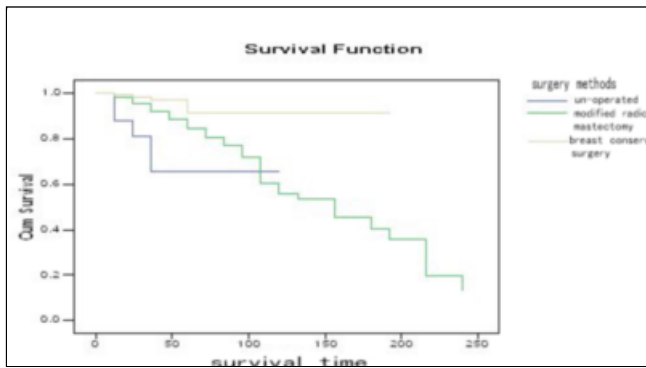


Figure 1: the relationship of surgery methods and survival rate.

Through the X^2 test chemotherapy group shows that great differences exist between the long-term survival rate and choice of chemo-therapy regimens ($P<0.05$). For example, the anthracycline combined with taxane regimen, which is frequently-used recently has an obvious advantage on the 5- and 10- survival rate accounts for 84.63% and 78.5% respectively and the median survival time is 240 months. The 10-year survival rate of the patients who receive chemotherapy regimen of anthracycline-based and free-taxane is lower than the former, which is 70.58% (figure 2). Distinct differences ($X^2=10.67$, $P=0.047$) were found after making a comparison of the Radiotherapy group and non- Radiotherapy group.

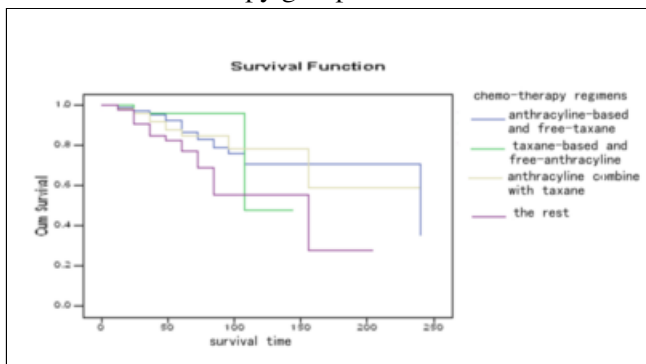


Figure 2: the relationship of chemo-therapy regimens and survival rate.

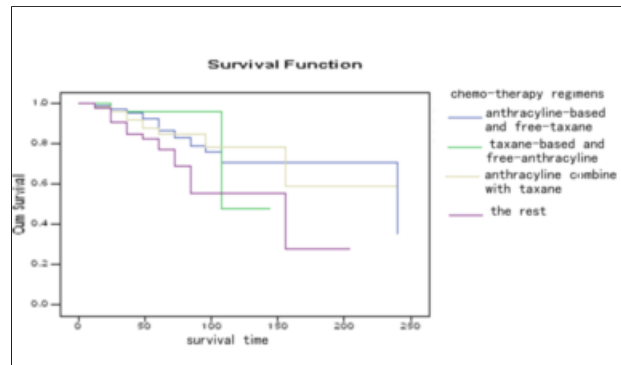


Figure 3: the relationship of radiation therapy and survival rate.

Discussions

In this decade, the recovery rate of breast cancer has significantly increased owing to the comprehensive treatment and introduction of interdisciplinary treatment. Except the surgery and radiation therapy, most of patients can receive systemic treatment. The progress of breast cancer treatment including the changes of treatment structure and education measures has obviously improved the prognosis of the cancer⁽²⁾. According to the data provided by the Cancer Research UK, the death rate was halved in the later 30 years after the patients’ age standardization in UK, down from 42/10000 at the end of 1980 to 24/10000 in 2012⁽³⁾.

Survival rate of the patients

The breast cancer is characterized by genetic heterogeneity and with different biologic features. The patients share the same diagnosis while distinctly different clinical prognosis. Compared with other types of cancer, the 5-year survival rate of the breast cancer is higher⁽⁴⁾, for example, in America, nearly 90% of the patients are still alive over 5 years after their diagnosis⁽⁵⁾. It’s very difficult to completely cure the metastatic tumors which include breast cancer, the treatment aims are restricted on prolonging the survival time of patients and improving their life quality (QOL)⁽⁶⁾.

In this study, the 5-year overall survival rate of the breast cancer is 80.64%, which approaches to the foreign studies-Vaneeuwaarde (79%)⁽⁷⁾ and Stebbing (80%)⁽⁸⁾.

Recently great advances have been achieved on the diagnosis and treatment of breast cancer, including the early diagnosis of breast cancer, neo-adjuvant chemotherapy, and breast conserving surgery, and the treatments of various pathological types and so on.

Surgery

The current treatment of breast cancer is mainly focus on the comprehensive treatment and the surgical excision is the major strategy for treatment. In Europe and the United States, the breast conserving surgery has become principal choice for the early breast cancer patients—more than 50% stage I and II patients receive breast conserving surgery. In China, however, the modified radical mastectomy is still a major mean for breast cancer and the breast conserving surgery is merely brought out in several hospitals.

In the past, the retrospective analyses of the surgical methods of the cancer are only limited to some big cities and have limitations restricted by region.

China has conducted massive breast cancer screening in recent years⁽⁹⁾, and early breast cancer cases account for a growing part of the total. The concepts of breast conserving surgery are gradually socially acceptable with the publicity and popularization of the science knowledge of the cancer. The differences of surgical methods choice between the developed areas in China and less developed areas have statistical significance. In China's eastern and southern areas, the rate of mastectomy (including Halsted radical mastectomy, modified radical mastectomy and total mastectomy) is on a declining trend and the rate of breast conserving surgery is on the rise. What's more, the changes in those two areas are more significant than the central and western areas of the country⁽¹⁰⁾.

The main reason that China is cautious about the breast conserving surgery is efficacy. The key to carry out the breast conserving surgery is to have the families informed and get their permission. In this group, the breast conserving surgery rate only accounts for 12.69%, which is lower than the 50% of the foreign countries; the 5-year survival rate of breast conserving surgery is 91.31%, which is higher than the 80.11% of the modified radical mastectomy. However, there is one reason that cannot be ignored the choice of surgery and methods is based on the TNM stage and patients' willingness. The breast conserving surgery usually has an earlier stage. Except a few patients give up breast conserving surgery for economic factors and other reasons, the reason why the others do not receive the surgery but accept endocrine therapy and palliative treatment is mostly because of late stage or old age, therefore, they all have low survival rates.

Chemotherapy regimens

Breast cancer is a systemic disease, the regional lymph nodes cannot act as an effective barrier to filter out cancer cells though they have important biological immune functions, by contrast, the blood flow is more helpful. Therefore, systemic chemotherapy is of great importance to the treatment. The analyses of randomized trials of EBCTCG⁽¹¹⁾ show that systemic adjuvant chemotherapy can cut the death rate by a third, in spite of other variables such as patient's age, tumor size, lymph nodes status, the expressions of hormone receptor and so on. The anthracycline drugs and taxoid chemotherapy drugs are two essential drugs of neo-adjuvant chemotherapy and adjuvant chemotherapy of the treatments⁽¹²⁾, especially the anthracycline drugs, which is a very common technique in clinic though it has much limitations. Some studies report that the anthracycline-based chemotherapy regimen is much more favorable to the breast tumor of a over-expression of HER-2⁽¹³⁾.

The chemotherapy regimen which based on anthracycline drugs has become a better choice for the over-expression of HER-2 and TNBC among the neo-adjuvant chemotherapy and adjuvant chemotherapy regimens. In addition, it has displayed better pathologic complete response in TNBC neo- adjuvant chemotherapy and higher survival rate in adjuvant chemotherapy. Davies⁽¹⁴⁾ finds that the 4-cycle anthracycline plus taxane chemotherapy can significantly low the death rate of the breast cancer according to the meta-analysis comparisons of 10000 patients' data in 123 large randomized clinical trials. Three pairs are included in the meta-analysis comparisons, one is the comparison of chemotherapy regimens between taxane plus anthracycline and non-taxane (n=44000); another is the comparison of chemotherapy regimens between anthracycline-based (n=7000) and CMF (Cyclophosphamide plus Methotrexate plus 5-fluorouracil, n=18000); the last is the comparison between the rest chemo-therapy regimens and non-chemotherapy treatments. It is also found that the anthracycline-based chemo-therapy regimens are superior to the standard CMF regimen. Compared with the non-chemotherapy treatment group, the CAF regimen, the standard 4AC regimen and the CMF regimen all have a lower death rate.

A large amount of meta-analyses indicate that the reduction in the mortality hazard ratio of taxane or anthracycline-based chemo-therapy regimens is barely affected by the age, lymph nodes status,

diameter and grade of tumor, hormonal-receptor status and the usage of TAM. The 10-year survival rate of the patients who receive chemotherapy is 1/3 higher than those who (the patients with estrogen receptor-positive cancers and receive hormonal therapy) do not receive the treatment. In the analysis, the 10-year survival rate of patients who are treated by the anthracycline combines with taxane chemotherapy regimen is 78.58%; the pure anthracycline-based treatment is 70.50% and the pure taxane-based treatment is 67.96%, which shows the drug combination can greatly improve the survival rate of the patients.

Radiation therapy

The postoperative radiation therapy can low the recurrence of local and regional lymph nodes. According to the EBCTCG's meta-analysis of 36 randomized trials in 1995, the radical mastectomy or the postoperative radiation of modified radical mastectomy can cut the recurrence of local and regional lymph nodes by 2/3. The systemic treatment, a combination of radiation therapy and chemotherapy after breast conserving surgery, which is a key point for the treatment. Radiation therapy is available to the pT1/T2N1 patients among the latest advances of the treatment of the breast cancer. Chang JS⁽¹⁵⁾ has carried out a disease-free survival (DFS) retrospective analysis of 1123 postoperative radiation therapy patients who have risk of low local recurrence during the period of 1998-2011. 692 patients who receive axillary lymph node dissection are enrolled in the study; most of the patients receive systemic chemotherapy and or hormonal therapy 17.8% of the total receives postoperative radiation therapy. The median follow-up duration is 98 months. All of the patients were divided into 2 groups. The division, which based on 2004, is bounded to the acceptance of modern mode treatment including sentinel lymph node biopsy, anthracycline or taxane-based chemotherapy and aromatase inhibitor. The results show that the patients' 5-year local recurrence of the group late-era is obviously lower than the group early-era, what's more, the 5-year DFS of the former rises significantly (the 5-year DFS of the former and the latter are 96.1% and 87.5% respectively).

Taking control of the all clinical pathological variables, the postoperative radiation therapy is the independent factor to improve DFS prominently. Standardized radiation therapy is of extreme usefulness in killing the remaining tumor lesions and

diminishing the local recurrence after the operation. Some researches show the transfer amount of axillary lymph nodes equal to or over 4 and the diameter of the tumor over 5cm are regarded as the undesirable high-risk factors of post-operative recurrence and prognosis. The post-operative chemotherapy or hormonal therapy have poorer functions on the reduction of local and regional lymph node recurrence for such patients, so radiation therapy is still an effective method and the postoperative radiation therapy is recommended to mainly radiate the chest and the supraclavicular region⁽¹⁶⁾.

According to the concepts of evidence-based medicine, ASCO recommends the postoperative chest radiated therapy as A-grade evidence⁽¹⁷⁾. The patients' 5-year survival rate in this group is 81.75%, which is higher than the 79.8% reported by the Vrijens and other analyses⁽¹⁸⁾. During the data collection, it is found that only few data record radiation region and total radiation dosage, for which some patients are not the in-patients or their initial diagnosis, surgery, radiation therapy and chemotherapy, are not conducted in the same hospital. The data that is not recorded in the clinical cases or clearly narrated by the families has not been dealt as radiation therapy in order to keep the preciseness of the data source.

Hormonal therapy

The 5-year hormonal therapy has greatly improved the 15-survival rate of a third of the estrogen receptor-positive breast cancer patients. High quality life during treatment, quite few pains, no need for particular preparation, nurse and prevention and wide acceptance are all the advantages of hormonal therapy drugs; the disadvantages include slow treatment effect, time-consuming to getting alleviation. The division of some tumor cells is inhibited after the application of hormonal therapy, and then they grow slowly, which is helpfully to slow down the development of the cancer. The drug action mechanism of antiestrogen manifests as the inhibition of combination of estrogen and ER during the process that drug combining with estrogen receptor. The common drugs are TAM, toremifene and raloxifene, the action mechanism of those drugs is to compete with the receptor of estradiol to form receptor complex. This receptor complex can reduce the activity of cancer cells. TAM adjuvant therapy, which can reduce the morbidity, mortality and occurrence probability of bilateral primary cancer, is always regarded as the golden standard of

hormonal therapy^(19,20).

Recently, many studies have proved that the 3rd aromatase inhibitors show a better clinical efficacy and provide more therapeutic regimens for clinic. Regan et al.⁽²¹⁾ conclude an evaluation on the hormone positive, post-menopausal, early stage breast cancer long-term recurrence and mortality risk through the randomized group analysis of 8010 patients. The median follow-up time is 8.1 years. 2459 patients are organized into TAM monotherapy group while 2463 patients are divided into letrozole monotherapy group randomly. 1540 patients are assigned to the 2-year letrozole sequential therapy of 3-year ATM, 1548 are assigned to 2-year letrozole sequential therapy of 3-year treatment. For the post-menopausal women with early stage breast cancer, the recurrent rate and fatality rate of letrozole monotherapy decline apparently compared with the TAM monotherapy.

There are no significant therapeutic differences between the TAM and letrozole sequential therapy group and letrozole monotherapy group. The present analysis has made no respective prognosis evaluation of hormonal therapy drugs. Due to the low price and wide acceptability, the patients who are with hormone-receptor-positive breast cancer at least have receive one hormonal therapy that the TAM represents. The untreated that has a poor prognosis can only be found among the receptor-negative subgroup. Besides, the present research has no statistical work of the influence that hormonal therapy put on the survival rate owing to the less detailed record and obscure narration of the families.

References

- 1) Bohm J, Zikan M. *Current knowledge of ductal carcinoma insitu*[J]. Ceska Gynecol, 2009, 74 (5): 339-47.
- 2) Scharl A, Kühn T, Papatthemelis T et al. *The Right Treatment for the Right Patient - Personalised Treatment of Breast Cancer*. Geburtshilfe Frauenheilkd. 2015 Jul; 75(7): 683-691.
- 3) Cancer research U K *Age-standardised mortality rates, females, UK, 1971-2012*. Online:<http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/mortality/uk-breast-cancer-mortality-statistics%23trendslast> access: 02.03.2015.
- 4) Soerjomataram I, Louwman MW, Ribot JG, et al. *An overview of prognostic factors for long-term survivors of breast cancer*. Breast Cancer Res Treat, 2008, 107: 309-330.
- 5) Blows FM, Driver KE, Schmidt MK, et al. *Subtyping of breastcancer by immunohistochemistry to investigate a relationshipbetween subtype and short and long term survival: A collaborative analysis of data for 10 159 cases from 12 studies*[J]. PLoS Med, 2010, 7(5): e1000279.
- 6) J Hara F, Kiyoto S, Takahashi M, et al. *Efficacy and safety of S-I in patients with metastatic breast cancer:retrospective reviewin a single institution*[J]. Oncology Epub. 2010, 79(3-4): 273-277.
- 7) Vaneeuwaarde RS, Vrede MA, Henar F'et al. *A nationwideanalysis of incidence and outcome of breast cancer in the conntlcyof Surinam,during 1994-2003*. Breast Cancer Res Treat, 2011.
- 8) Stebbing J, Delaney G, Thompson A. *Breast cancer(non-metastatic)*[J]. Clin Evid (Online), 2011, pii: 0102.
- 9) Zhang Baoning. *The Clinical Application Status and the Development Trend of Breast Conserving Surgery*. Chinese Journal of Practical Surgery, 2008, 28: 23-524.
- 10) Zhang Baoning, Zhang Bin, Tang Zhonghua, et al. *10-year Changes and Development of Surgical Treatment for Breast Cancer in China* [J]. Chinese Journal of Oncology, 2012, 34[8]: 582-587.
- 11) Peto R, Davies C, Godwin J, et al. *Early Breast Cancer Trialists' Collaborative Group (EBCTCG) . Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials*. Lancet. 2012; 379: 432-444. [PMC free article] [PubMed].
- 12) Anbok Lee, Woosung Lim, Byung-In Moon. *Chemotherapy response assay test and prognosis for breast cancer patients who have undergone anthracycline and taxane-based chemotherapy*[J]. J Breast Cancer, 2011, 14(4): 283-288.
- 13) Yi SY, Ahn JS, Uhm JE, et al. *Favorable response to doxorubicincombination chemo- therapy does not yield good clinical outcomein patients with metastatic breast cancer with triple Begative phenotype*[J]. BMC Cancer, 2010, 10(5).
- 14) Davies C, Godwin J. *Comparisons between different polychemotherapyregimens for early breast cancer:meta-analyses of long-term outcome among 100 000 women in 123 randomised trims*[J]. Lancet, 2012, 379(9814): 432.444.527.
- 15) Chang JS1, Lee J, Kim KH, et al. *Do Recent Advances in Diagnostic and Therapeutic Procedures Negate the Benefit of PostmastectomyRadiotherapy in N1 Patients With a Low Risk of Locoregional Recurrence?* Medicine(Baltimore). 2015 Aug; 94(33): e1259.doi: 0.1097/MD.0000000000001259.
- 16) Gu Xianzhi, *Radiation Oncology*. Beijing: Beijing Union Medical University Press, 2008. 1178-1180.
- 17) Abram Recht, Stephen BE, Lawrence J, et al. *Pastmastectomy of Clinical Oncology*. J Clin Oncol. 2001.19(5): 1539.
- 18) Vrijens F' Stordeur S' Beirens l' et al. *Effect of hospital volumeon processes of care and 5-year survival after breast cancer.A population-based study on 25000 women*[J]. Breast, 2011, 26(5): 284-289.
- 19) Davies C, Godwin J, Gray R, et al. *Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen:patient-level meta-analysis of randomised trials*. Lancet. 2011;3 78: 771-784.
- 20) Stephen Jones. *The Circuit Reports of the Treatment*

Strategies of Hormonal therapy of Breast Cancer[N].
China Medical Tribune, 2009, 1210(6).

- 21) Regan MM, Neven P, Giobbie-Hurder A, et al.
Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 randomised clinical trial at 8.1 years median follow-up[J].
Lancet Oncol, 2011, 12(12): 1101-1108.

Abbreviations:

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group)
2. ER (estrogen receptor)
3. TAM (tamoxifen)
4. CAF (CTX+ADM+5-Fu)
5. 4AC (4 Cycles ADM+CTX)
6. ASCO (American Society of Clinical Oncology)
7. HER-2 (human epidermal growth factor receptor-2)
8. TNBC (Triple Negative Breast Cancer)
9. SPSS13.0 (The complete data applies SPSS13.0 statistics software analysis processing)

Corresponding author

MU HONG-CHAO

The People's Liberation Army 404th Hospital 264200
(China)