

## RESEARCH COMMUNICATION

# Validation of Treatment Efficacy of a Computer-assisted Program for Breast Cancer Patients receiving Postoperative Adjuvant Chemotherapy

Yong Jiang<sup>1,2#</sup>, Xin-En Huang<sup>1,2#\*</sup>, Peng-Wei Yan<sup>1,2</sup>, Lin Cui<sup>3</sup>, Jin-Hai Tang<sup>4</sup>, Jin Xiang<sup>5</sup>

### Abstract

**Aim:** To validate the clinical value of a computer assisted program (CAP), (visit website; <http://xinenhuang.blog.sohu.com> for details) for breast cancer patients who receive postoperative adjuvant chemotherapy. **Methods:** Patients with histologically confirmed breast cancer after mastectomy who received postoperative chemotherapy in Jiangsu Cancer Hospital and Research Institute were recruited in this study. All eligible patients are divided into three groups: group A, regimen of practical chemotherapy consistent with CAP prediction; group B, partly consistent with CAP prediction; group C, inconsistent with CAP prediction. Overall survival (OS) was compared among groups A, B and C to determine the efficacy of CAP. **Results:** From November 1992 to July 2007, 310 female breast cancer patients were recruited into this study, with 112, 106 and 89, respectively, in groups A, B, and C. Prognosis of group A was better than both group B and C, with significantly different survival curves between group A and B ( $p=0.0004$ ) and group A and C ( $p=0.0046$ ). **Conclusion:** Validation showed our CAP to provide clinically valuable information on adjuvant chemotherapy for postoperative breast cancer patients.

**Keywords:** Breast cancer - medical software - postoperative chemotherapy - overall survival

*Asian Pacific J Cancer Prev*, 11, 1059-1062

### Introduction

According to the American Cancer Society (ACS) statistics, breast cancer is the most common malignancy in the United States (Jemal et al., 2008). In China, the incidence of breast cancer increased year by year, and at present is the most common female malignancy in Beijing, Tianjin, and Shanghai (Linos et al., 2008; Ziegler et al., 2008; Shanghai Municipal Government). The incidence of breast cancer has increased steadily, but breast cancer mortality appears to be declining in the United States over the past few decades (Early Breast Cancer Trialists' Collaborative Group, 2005; Jemal et al., 2008) suggesting a benefit from early detection and more effective treatment. In addition to local therapy, systemic treatment improves disease-free and overall survival (DFS and OS) in patients with early breast cancer. Based on well established prognostic markers, such as age, tumor grade/size and nodal status, postoperative patients are classified into different risk groups to determine who will benefit from adjuvant chemotherapy. On this background, Xin-En Huang of the Department of Chemotherapy in Jiangsu Cancer Hospital and Research Institute developed a computer assisted program (CAP)

based on clinical and laboratory parameters to recommend postoperative chemotherapy for breast cancer patients. By entering age, tumor size, tumor grade, number of lymph node metastases, vascular permeation, estrogen receptor/progesterone receptor (ER/PR) status, and human epidermal growth factor receptor 2 (HER-2) status (Wolff et al., 2007) into the interface of this software, a regimen including chemotherapy, endocrine therapy, molecular targeted therapy, or clinical observation can be displayed (see <http://xinenhuang.blog.sohu.com> for details). The aim of the present study was to validate the clinical value of CAP by comparing survival of breast cancer patients treated in Jiangsu Cancer Hospital.

### Materials and Methods

#### Study population

From November 1992 to July 2007, postoperative breast cancer patients with histologically confirmed diagnosis and received adjuvant chemotherapy in Jiangsu Cancer Hospital and Research Institute were considered eligible if they met the following criteria: with whole medical record, including; age at diagnosis, tumor size, histological type, number of lymph node metastasis,

<sup>1</sup>Department of Chemotherapy, <sup>4</sup>Department of General Surgery, <sup>5</sup>Department of Scientific Research, Jiangsu Cancer Hospital & Research Institute; <sup>2</sup>Nanjing Medical University, Nanjing, <sup>3</sup>Department of Chemotherapy, Jiangyan People's Hospital, Jiangyan, China, # co-first author, \*For correspondence: [huangxinen06@yahoo.com.cn](mailto:huangxinen06@yahoo.com.cn)

vascular permeation, ER/PR status, HER-2 expression and survival time, and Karnofsky Performance Score (KPS) >60, life expectancy >3 months, adequate bone marrow reserve (leukocyte count  $\geq 4.0 \times 10^9/L$ , platelet count  $\geq 100 \times 10^9/L$ ), adequate liver and renal function (bilirubin level  $\leq 1.5$  mg/dL, alanine aminotransferase/aspartate aminotransferase < 2 times the upper limit of normal, creatinine level  $\leq 1.5$  mg/dL). A written informed consent could be obtained from patient before surgery and chemotherapy. All patients who were eligible to this study were hospitalized at Jiangsu Cancer Hospital and Research Institute. The facility is located in Nanjing, China, and is a central Cancer Hospital in Jiangsu Province with 1200 hospital beds. It serves about 80 million people of Jiangsu Province and neighboring regions. General information on this area can be found on the website: <http://english.peopledaily.com.cn/data/province/jiangsu.html>.

*Computer assisted program (CAP)*

Software was based on clinical and laboratory parameters to predict postoperative treatment for patient with breast cancer. By entering age, tumor size, tumor grade, number of lymph node metastasis, vascular permeation, ER/PR status and HER-2 expression into the interface of this software, treatment including postoperative adjuvant chemotherapy, endocrine therapy, molecularly targeted therapy can be predicted. The chemotherapy regimens included in the software mainly consist of doxorubicin 60mg/m<sup>2</sup> intravenous injection (iv) day 1 (d1) + cyclophosphamide 600mg/m<sup>2</sup> iv d1 (AC chemotherapy cycled every 21 days) (Fisher et al., 1990), epirubicin 60-90mg/m<sup>2</sup> iv d1 + cyclophosphamide 600mg/m<sup>2</sup> iv d1 (EC chemotherapy cycled every 21 days) (Piccart et al., 2001), docetaxel 100mg/m<sup>2</sup> iv d1 (or paclitaxel 135-175mg/m<sup>2</sup> iv d1) + doxorubicin 60mg/m<sup>2</sup> iv d1 (or epirubicin 60-90mg/m<sup>2</sup> iv d1) + cyclophosphamide 500mg/m<sup>2</sup> iv d1 (D/TAC or D/TEC chemotherapy cycled every 21 days) (Martin et al., 2005), cyclophosphamide 600mg/m<sup>2</sup> iv d1 + methotrexate 40mg/m<sup>2</sup> iv d1 + fluorouracil 500mg/m<sup>2</sup> iv d1 (CMF chemotherapy cycled every 21 days) (Goldhirsch et al., 1998). Endocrine therapy includes “tamoxifen 10mg oral medication twice a day” continued to 5 years (Coates et al., 2007). Molecular targeted therapy postoperatively consists of trastuzumab 4 mg/kg iv d1 followed by 2 mg/kg iv weekly (Cobleigh et al., 1999; Joensuu et al., 2006). The software can be viewed on the website: <http://xinhuanang.blog.sohu.com>.

Group A: practical regimen is totally consistent with that predicted by CAP; group B: regimen of chemotherapy is partly consistent with CAP predication; group C: regimen of chemotherapy is inconsistent with CAP predication.

*Statistical methods*

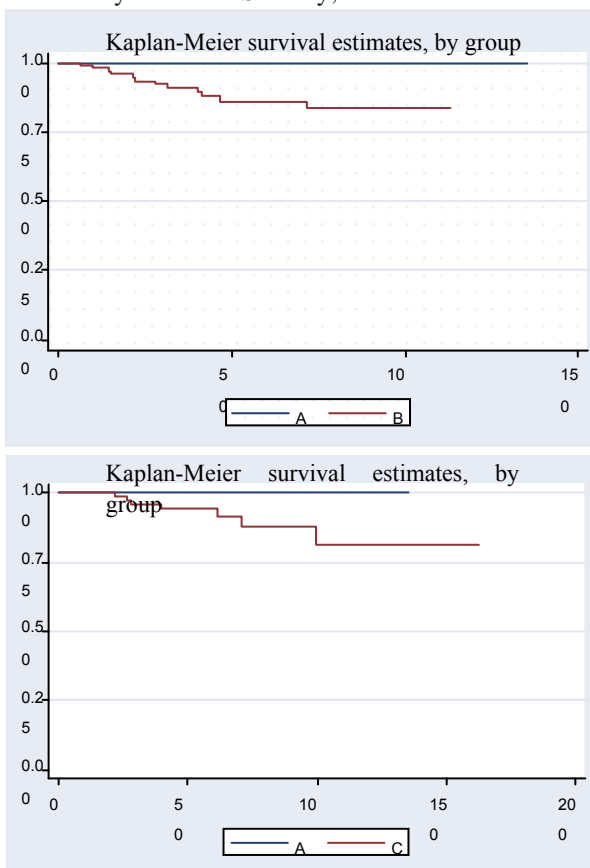
All statistical analyses were performed using STATA software, version 8.0 (Stata Corporation, 4905 Lakeway Drive College Station, Texas 77845 USA). Survival analysis was performed by the Kaplan-Meier method. Statistical significance was evaluated using the log-rank test and set at  $p < 0.05$ . Survival time was determined from cancer diagnosis to death or to the date of last follow-up

**Table 1. Patient Demographics and Tumor Characteristics**

Characteristics	Overall	Group A	Group B	Group C
No. of patients	310	102	115	93
Mean age at diagnosis	49	47	50	50
Mean survival, month	48	55	41	55
Tumor size				
<2cm	75	39	11	25
$\geq 2$ cm	235	63	104	68
Tumor grade				
Grade I	10	3	3	4
Grade II	286	97	102	87
Grade III	14	2	10	2
Positive lymph node status				
<4	283	99	103	81
$\geq 4$	27	3	12	12
ER/PR status				
Negative	98	16	51	31
Positive	212	86	64	62
HER-2 status <sup>#</sup>				
- or +	277	95	100	82
++	16	3	10	3
+++	17	4	5	8
Vascular permeation				
Negative	292	95	109	88
Positive	18	7	6	5

<sup>#</sup>immunohistochemical test

contact. Dates of death were obtained and cross-checked using at least one of the following methods: by a telephone call; inpatient and outpatient medical records; documents of Ministry of Public Security; and confirmation from a



**Figure 1. Overall Survival Kaplan-Meier Curves.** a) Group A versus group B,  $P=0.0004$ ; b) group A versus group C,  $P=0.0046$

patient family member. The process of data collection was conducted in compliance with the ethical requirements of each of the participating patients.

## Results

### Patient characteristics

From November 1992 to July 2007, 310 female breast cancer patients were recruited in the study. Numbers of patients in group A, B, and C are 102, 115 and 93. All patients were followed until February 25, 2008. At the end of follow-up, 19 patients had died. The mean years of age at diagnosis of group A, group B and group C is 47, 50 and 50 respectively. The mean survival time of group A, group B and group C is 54.8, 41.3, and 54.7 months respectively. Characteristics of 310 patients are illustrated in Table 1.

### Survival analysis

From Figure 1, there was significant difference in OS between group A, and B or C. Group A had better OS than both group B ( $p=0.0004$ ) and C ( $p=0.0046$ ).

## Discussion

St. Gallen (Goldhirsch et al., 2009) and NCCN clinical practice guidelines in oncology (National Comprehensive Cancer Network: <http://www.nccn.org/index.asp>) are commonly used to guide clinical practice in treating patients with breast cancer. Recently, it is reported that Adjuvant! Online (Ravdin et al., 2001; Olivotto et al., 2005), DNA microarray technology (Jeffry et al., 2005), Mammprint assay (van 't Leer et al., 2002), and 21-gene assay (Oncotype Dx) (Paik et al., 2004; 2006; Fan et al., 2006) could also provide important information in predicting individual prognosis and treatment in this setting. For example, the Mammprint assay uses microarray technology to analyze a 70-gene expression profile from frozen breast tumor tissue as a means of selecting patients with early-stage, node-negative breast cancer who are more likely to develop distant metastases (van der Vijver et al., 2002; Glas et al., 2006; Mook et al., 2007), and a validated computer based model (Adjuvant! Online; [www.adjuvantonline.com](http://www.adjuvantonline.com)) is available to estimate 10-year disease-free and overall survival. These technologies aid the clinician to estimate the absolute benefits from systemic adjuvant therapy, and may also be utilized by patients in their shared decision-making regarding the toxicities, costs, and benefits of therapy. However, these technologies could not provide concrete regimens, which is complex and varied in real practice. In many situations, physician and patient try to jointly explore and select a most appropriate option from available chemotherapeutic regimens according to risk factors of the disease. In fact, a number of combination chemotherapeutic regimens could be appropriate when postoperative adjuvant chemotherapy is considered. Whether or not to recommend an adjuvant treatment and how to select an appropriate treatment, mainly depend on the decision of a doctor, so there will always be subjective errors. Consequently, inadequate treatment or overtreatment always occurs. Through survival analysis of

310 breast cancer patients in our study, it demonstrates that CAP can assist making an objective decision, prolonging the survival of breast cancer patients and greatly avoiding inadequate treatment or overtreatment. However, we concern that all our study patients are Chinese women with breast cancer, it is not known whether CAP is applicable to patients of other countries and races. So we look forward to conducting more validation studies with larger sample size, and to expanding the range of applications, from neo-adjuvant chemotherapy, radiotherapy to palliative care in the future. In conclusions, our validation study confirms that CAP provides important information for clinicians, and CAP has a very strong clinical value.

## Acknowledgements

This work was supported in part by a grant from the Department of Personnel of Jiangsu Province (Liu Da Ren Cai Gao Feng Project 2#); Organization Department of Jiangsu Provincial Party Committee, Talent Work Leading Group of Jiangsu Province (333 High-level Talents Training Project); Special funds for research projects of Jiangsu Cancer Hospital and Research Institute (ZK200805); Kang Lai Te clinical research funds of Department of Health of Jiangsu Province (P200908).

## References

- Coates AS, Keshaviah A, Thürlimann B, et al (2007). Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. *J Clin Oncol*, **25**, 486-92.
- Cobleigh MA, Vogel CL, Tripathy D, et al (1999). Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J Clin Oncol*, **17**, 2639-48.
- Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*, **365**, 1687-717.
- Fan C, Oh DS, Wessels L, et al (2006). Concordance among gene-expression based predictors for breast cancer. *N Engl J Med*, **355**, 560-9.
- Fisher B, Brown AM, Dimitrov NV, et al (1990). Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with six months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: Results from NSABP B-15. *J Clin Oncol*, **8**, 1483-96.
- Glas AM, Floore A, Delahaye LJ, et al (2006). Converting a breast cancer microarray signature into a high-throughput diagnostic test. *BMC Genomics*, **7**, 278-87.
- Goldhirsch A, Colleoni M, Coates AS, et al (1998). Adding adjuvant CMF chemotherapy to either radiotherapy or tamoxifen: are all CMFs alike? The International Breast Cancer Study Group (IBCSG). *Ann Oncol*, **9**, 489-93.
- Goldhirsch A, Ingle JN, Gelber RD, et al (2009). Threshold for therapies: highlights of the Sankt Gallen international expert

- consensus on the primary therapy of early breast cancer 2009. *Ann Oncol*, **20**, 1319-29.
- Jeffrey SS, Lonning PE, Hillner BE (2005). Genomics-based prognosis and therapeutic prediction in breast cancer. *J Natl early breast cancer. J Clin Oncol*, **23**, 2716-25.
- Mook S, Van't Veer LJ, Rutgers EJ, et al (2007). Individualisation of therapy using Mammaprint: from development to the MINDACT trial. *Cancer Genomics Proteomics*, **4**, 147-55.
- Paik S, Shak S, Tang G, et al (2004). A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med*, **351**, 2817-26.
- Paik S, Tang G, Shak S, et al (2006). Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol*, **24**, 3726-34.
- Piccart MJ, Di Leo A, Beauduin M, et al (2001). Phase III trial comparing two dose levels of Epirubicin combined with cyclophosphamide with cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer. *J Clin Oncol*, **19**, 3103-10.
- Ravdin PM, Siminoff LA, Davis GJ, et al (2001). Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. *J Clin Oncol*, **19**, 980-91.
- Shanghai Municipal Government; Shanghai cancer rate is nation's highest: 350 per 100,000 people. Available at: <http://www.shanghai.gov.cn/shanghai/node23919/node23923/userobject22ai37366.html>
- National Comprehensive Cancer Network: <http://www.nccn.org/index.asp>
- van der Vijver MJ, He YD, van't Veer LJ, et al (2002). A gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med*, **347**, 1999-2009.
- van 't Veer LJ, Dai H, van de Vijver MJ, et al (2002). Gene expression profiling predicts clinical outcome of breast cancer. *Nature*, **415**, 530-6.
- Wolff AC, Hammond ME, Schwartz JN, et al (2007). American Society of Clinical Oncology; College of American Pathologists. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol*, **25**, 118-45.
- Ziegler RG, Anderson WF, Mitchell HG (2008). Increasing breast cancer incidence in China: the numbers add up. *J Natl Cancer Inst*, **100**, 1339-41.