Original Study

Adherence to Needed Adjuvant Therapy Could Decrease Recurrence Rates for Rural Patients With Early Breast Cancer

Qijia Xuan,¹ Kun Gao,¹ Ying Song,¹ Shu Zhao,¹ Lina Dong,¹ Zhongbai Zhang,² Qingyuan Zhang,¹ Jingxuan Wang¹

Abstract

This study suggests that later stage upon diagnosis and nonadherence to treatment contribute toward worse breast cancer outcomes among rural patients with breast cancer. Adherence to adjuvant therapy could decrease recurrence rates for rural patients with early breast cancer.

Purpose: The purpose of this study was to evaluate the differences in stage upon diagnosis, adherence to adjuvant treatment, and recurrence between rural and urban patients with early breast cancer. **Methods:** This retrospective study included 3640 patients with primary breast cancer recruited from 2000 to 2009. Patients who developed recurrence or metastasis were verified by adequate diagnostic imaging modalities and pathology. The χ^2 test was used to compare groups with respect to variables (recurrence and clinicopathologic features). A multivariable Cox proportional hazard regression model was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for breast cancer recurrence risk. **Results:** Compared with tumors in urban patients, those in rural patients showed higher histologic grade, larger size, more lymphatic metastasis, and higher Ki-67 index; therapy adherence was strongly associated with recurrence in both. Compared with urban patients, the female rural patients had a higher recurrence rate. However, no significant difference in recurrence rates was observed between urban and rural patients following guideline adherence. **Conclusions:** The results of our study suggest that the later stage upon diagnosis and non-adherence to treatment contribute toward worse breast cancer outcomes among rural patients with breast cancer. Adherence to needed adjuvant therapy could decrease recurrence rates for rural patients with early breast cancer.

Clinical Breast Cancer, Vol. ■, No. ■, ■-■ © 2016 Elsevier Inc. All rights reserved.

Keywords: Adherence, Breast cancer, Recurrence rate, Rural, Urban

Introduction

A total of 495,069 new cancer cases were reported in the latest Chinese Cancer Registry Annual Report. Among these, 59.35% were from urban areas, and 40.65% were from rural areas. Tumor burdens dramatically differ in urban and rural areas. However, whether in urban or rural areas, breast cancer has become the most

Q.X. and K.G. contributed equally to this work as first authors.

Q.Z. and J.W. contributed equally to this work.

Submitted: Feb 2, 2016; Revised: Jul 18, 2016; Accepted: Jul 20, 2016

Addresses for correspondence: Qingyuan Zhang, PhD or Jingxuan Wang, PhD, Department of Medical Oncology, The Tumor Hospital of Harbin Medical University, 150 Haping Rd, Nangang District, Harbin 150040, China E-mail contact: zqyxsci@126.com; wjxilywendy@126.com

common cancer among Chinese women. The incidence of breast cancer is significantly higher in urban areas than in rural areas $(39.47/10^5 \text{ vs. } 25.28/10^5)$, whereas the mortality to incidence ratio is dramatically higher in diagnosed rural women compared with urban women (mortality to incidence ratio: 0.26 vs. 0.23).

A substantial reduction in breast cancer mortality has been observed in developed countries over the past 2 decades, and this has been attributed to early diagnosis with widespread use of screening mammography and breast ultrasound. ^{2,3} Evidence exists that rural women have difficulty in receiving breast mammograms, which facilitate early cancer detection. ⁴ Except for early diagnosis, adequate treatments offer the best chance of reducing mortality. ⁵ Considering the life span of women with this disease, breast cancer can be thought of as a chronic condition. Patients with breast cancer need to receive a combination of treatments, including surgery, radiation therapy, chemotherapy, and endocrine therapy; patients attain only maximum therapy benefits if they follow

 $^{^1\}mathrm{Department}$ of Medical Oncology, The Tumor Hospital of Harbin Medical University, Harbin, China

²Logistics University of People's Armed Police Force, Tianjin, China

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Adherence to Therapy Could Decrease Recurrence Rate

Table 1

Inclusion Criteria for Guideline Adherence Based on the Breast Cancer Diagnostic and Treatment Practices of China Regarding Radiotherapy, Chemotherapy, and Endocrine Therapy

Conforming to Suggested Adjuvant Therapy

Chemotherapy

NO

Age <35 years, T >2 cm, GII-GIII, HER2+ or ER/PR-

N1

Premenopausal patients and postmenopausal patients without good prognosis factors (HER2 $^-$, ER/PR $^+$, T \leq 0.5 cm, or Gl)

N2-N3

Radiotherapy

Radiotherapy

Lumpectomy

Except for age >70 years, ER/PR⁺ or stage I of TNM classification

Mastectomy ± reconstruction

Tumor >5 cm or tumor direct extension to the chest well and/or to the skin. Positive axillary nodes >4.

T1, T2, or N1 with any of these high risk factors (age ≤40 years, ER/PR⁻, HER2⁺, the number of lymph node dissection is not complete, or the ratio of metastatic lymph node >20%).

Endocrine therapy

Endocrine therapy

Hormone receptor positive-status

Premenopausal at diagnosis

- 1. Tamoxifen for 5 years.
- 2. Tamoxifen + ovarian suppression or ablation.
- Tamoxifen ± ovarian suppression or ablation for 2-3 years in premenopausal patients, then switch to an aromatase inhibitor for 2-3 years when these patients are in postmenopausal periods in order to complete at least 5 years of endocrine therapy.

Postmenopausal at diagnosis

- 1. Aromatase inhibitor for 5 years.
- Tamoxifen for 5 years for the women with a contraindication to aromatase inhibitors, who decline aromatase inhibitors, or who are intolerant of the aromatase inhibitors.

Non-conforming to Suggested Adjuvant Therapy

Overtherapy

NO

Without high recurrence risks

N.

Postmenopausal patients with good prognosis factors (HER2 $^-$, ER/PR $^+$, T <0.5 cm, or GI)

Undertherapy

Not take suggested adjuvant chemotherapy, not complete the breast cancer diagnostic and treatment practices recommended number of cycles of treatment, or delay the initiation of adjuvant chemotherapy (>60 d). 35,a

Overtherapy

Mastectomy ± reconstruction

NO with tumor \leq 5 cm

T1, T2, or N1 without any of these high risk factors (age ≤40 years, ER/PR[−], HER2⁺, the number of lymph node dissection is not complete, or the ratio of metastatic lymph node >20%).

Undertherapy

Not take suggested adjuvant radiotherapy, not take enough dose or delay the initiation of adjuvant radiotherapy (>90 d).^a

Overtherapy

Hormone therapy in hormone receptor-negative patients.

Undertherapy

- Aromatase inhibitor for hormone receptor-positive premenopausal patients at diagnosis.
- Not take suggested adjuvant therapy, delay the initiation of adjuvant endocrine therapy (>180 d), or with an adherence index less than 80%.^b

Abbreviations: ER = estrogen receptor; G = grade; HER2 = human epidermal growth factor receptor 2; PR = progesterone receptor.

^aThe time gap to adjuvant chemotherapy and radiation therapy was defined as number of days from the most definitive operation for the breast cancer to the first administration of chemotherapy or radiation therapy.

^bRecords for each individual patient were then used to calculate an adherence index across the entire duration of therapy, up to 5 years, based on the total days covered by all prescriptions and their duration of use. Patients with an adherence index less than 80%, the cut-off value widely used in previous studies, were deemed to have low adherence.

instructions and adhere to dosing schedules. A few clinical research studies have confirmed that guideline-adherent treatment could improve survival rates of patients with breast cancer, particularly for triple-negative, bilateral breast cancer, or young (< 35 years) patients with breast cancer. However, rural women among indigenous and/or minority groups are more likely to show non-adherence to the treatments for breast cancer if they had surgery, radiation therapy, chemotherapy, endocrine therapy, or a combination of any or all of the above, and these factors are known to increase risks of breast cancer recurrence and mortality. 9

Numerous studies have examined the possible urban-rural disparities in breast cancer; however, the findings have been mixed.

Urban/rural residence had no significant association with cancer stage for breast cancer in California. However, some studies suggested a reverse pattern of rural-urban disadvantage, in which late-stage risk is higher in cities than in rural areas. However, in China, appointment and grading treatment systems have yet to be widely established. Heilongjiang Province is one of the developing areas in China. The province is located in the northeast part of the country with a population of more than 38 million, 44.5% of which are rural (according to the results of Bureau of Heilongjiang Province in 2010); most of them are residents of remote and impoverished rural areas. We conducted this study to evaluate which, between later stage upon diagnosis or nonadherence with

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