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Original article

Identify high risk estrogen receptor-positive breast cancer patients for extended endocrine therapy

JunJie Li [a, b, 1], Yizhou Jiang [a, b, 1], Yirong Liu [a, b], Zhimin Shao [a, b, *]

[a] Department of Breast Surgery, Fudan University Shanghai Cancer Center, Fudan University, Shanghai, People's Republic of China
[b] Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, People's Republic of China

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ABSTRACT

Purpose: To demonstrate the patterns of breast cancer-specific mortality (BCSM) in estrogen receptor (ER)-positive diseases and to identify high-risk candidates for extended endocrine therapy.
Methods: Using the Surveillance, Epidemiology and End Results database, we identified ER-positive patients diagnosed between 1990 and 2000 (cohort 1 [C1]) and between 2001 and 2005 (cohort 2 [C2]). The patterns of BCSM were calculated using Cox proportional hazard regression models. A risk classification model was developed, and X-tile software was used to divide patients with high BCSM rates into 3 risk groups.
Results: The annual BCSM rate of C2 was decreased by one-third and was maintained at 10–15 (per 1000 persons per year) from year 2 to year 10. Long-term mortality risks still persisted in C2, especially in patients with node-positive, grade 3 or T3 disease, who should be considered as "clinical-high-risk". These patients were further divided into 3 risk groups through our model: for C1, 42.2% were in the low-risk group, 38.9% in the medium-risk group, and 18.9% in the high-risk group; and for C2, 45.5% were in the low-risk group, 38.2% in the medium-risk group and 16.2% in the high-risk group ($p < 0.001$). The BCSM rates of the patients in each group within C2 decreased, and fewer patients in C2 were classified into the clinical high-risk group.
Conclusion: ER-positive patients with node-positive, grade 3 or T3 diseases had sustained risks of death throughout the 10-year time frame, and our model is helpful to identify patients with high risk who are candidates for extended endocrine therapy.

1. Introduction

Breast cancer is the most common cancer among women worldwide, and approximately two-thirds of cases are estrogen receptor(ER)-positive. Patients with ER-positive breast cancer have a sustained risk of disease recurrence and death for at least 15 years after 5 years of adjuvant Tamoxifen therapy [1]. The results of the ATLAS and MA.17 trials showed that in women with ER-positive disease, the extension of endocrine therapy to 10 years rather than treatment for 5 years, produces a further reduction in recurrence and mortality [2,3]. According to the current St Gallen International Expert Consensus, the following patients should continue to receive endocrine therapy for 10 years: patients whose cancers are initially node-positive, those with grade 3 diseases, those whose cancers express high levels of Ki-67, and patients who are premenopausal at baseline who become postmenopausal during the 5 years of Tamoxifen therapy [4].

In addition to specific clinical and pathological features, multigene expression signatures are clinically available for the improvement of the risk-benefit of extended adjuvant endocrine therapy for late recurrence in patients with ER-positive breast cancer. An example is the breast-cancer index (BCI), which would classify 15–20% patients (who remained free of distant recurrence for 5 years) as high risk for late distant recurrence; these patients would have a 10-year distant recurrence-free survival of 85%–89.9% and might benefit from extended endocrine therapy [5,6]. However, currently the clinician should not make decisions based on such assays because there is no consensus about how low the annual risk of recurrence should be to avoid extended adjuvant endocrine therapy [7].

* Corresponding author. Department of Breast Surgery, Fudan University Shanghai Cancer Center, 270 Dong-An Road, Shanghai, 200032, People's Republic of China.
E-mail address: zhimingshao@yahoo.com (Z. Shao).
[1] JJ Li and YZ Jiang contributed equally to this work.

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The absolute risk reductions that result from endocrine therapy depend on the absolute breast cancer risks. However, through a combination of early detection and more effective treatments, the mortality rate has decreased over the last three decades in most Western countries [8,9].The number of patients who remain in the high-risk category and the ways in which these patients can be identified are still unknown. In the present analysis, we analyzed the breast cancer-specific mortality (BCSM) among patients with ER-positive cancer who were treated from 1990 to 2000 and from 2001 to 2005. The purpose of this was to demonstrate the current patterns of BCSM and to identify the amount of patients at a high risk of late death that might benefit from extended endocrine therapy in the modern treatment era.

2. Materials and methods

2.1. Patient selection and outcome measures

Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) cancer database, which consists of 18 population-based cancer registries, were used in the present study. Female patients with invasive breast cancer who were diagnosed between January 1, 1990, and December 31, 2005, were included for further analysis. According to different time periods of diagnosis, we divided the eligible patients into two cohorts, as follows: cohort 1 (C1) consisted of patients who were diagnosed between January 1, 1990, and December 31, 2000, and cohort 2 (C2) consisted of patients who were diagnosed between January 1, 2001, and December 31, 2005. Patients who were diagnosed before 1990 were excluded due to unavailable hormone receptor data, and patients who were diagnosed after 2005 were excluded to ensure adequate follow-up time.

In all, 145,813 patients were included in the present study according to the following inclusion criteria: female, pathologically confirmed invasive ductal carcinoma (IDC, ICD-O-3 8500/3), age at diagnosis between 20 and 84 years, surgical treatment that consisted of either mastectomy or breast-conserving surgery, cancer classified as American Joint Committee on Cancer (AJCC) stages I to III, unilateral breast cancer, positive status of ER, known time of diagnosis, and breast cancer as the first and only cancer diagnosis (Fig. 1). Information on the following variables was obtained if available: tumor size, histological grade, race, marital status, and whether the cancer was treated with radiotherapy. BCSM was the primary study outcome, calculated from the date of diagnosis to the date of death from breast cancer. Patients who died of other causes were censored on the date of death.

This research was submitted to the Ethical Committee and Institutional Review Board at the Shanghai Cancer Center of Fudan University and was determined to be qualified for institutional review board exemption. The release of data through the SEER database does not require informed patient consent because cancer is a reportable disease in every state in the US.

2.2. Data management and statistical analysis

Age was categorized into 3 groups: <40, 40–60, and ≥60 years of age. Race and ethnicity were coded as white, black, or other (American Indian/AK Native, Asian/Pacific Islander). Marital status was coded as married or not married. Tumor characteristics included tumor size, histological grade, lymph node status, PR status, and whether radiotherapy was given.

The median follow-up times were 154 months and 103 months for C1 and C2, respectively, all analyses in the present study were conducted in a 10-yr frame to guarantee the validity and reliability of the results. All factors were treated as constant in the multivariate regression analysis. Cox proportional hazard regression models were applied to estimate the hazard ratios in the different subgroups [10–12]. To further explore the effects of prognostic factors on survival in different time periods, we hypothesized that the effects changed with time, as previously reported [10,12]. Therefore, when we calculated a time-dependent effect, flexible parametric survival models were used to model the outcomes, which allows covariates to have time-dependent effects by using spline functions [10,12,13]. The BCSM, the differences in mortality rates and hazard ratios were estimated using the default parameters setting in the flexible models [11]. The baseline rates were estimated using a spline with five degrees of freedom, as previously stated [12].

2.3. Exploratory analysis in “clinical-high-risk” patients

Patients with positive lymph nodes, grade 3 or T3 tumor size, were considered high-risk candidates for extended endocrine therapy. To better understand the clinical outcome of this group of patients and to aid in personalized treatment decisions, we further analyzed those patients in greater detail. Cox multivariable hazard regression models were used to assess the factors' effect on survival outcome from five to ten years' follow-up time frame, age, race, grade, tumor size, node status and receptor status were all included. Based on these models, we developed a risk classification formula. Each level of every factor that was included in the formula had a corresponding value. Accordingly, the risk score of all included patients could be calculated. Patients with a follow-up time of less than five years, regardless of whether they died or were censored, were not eligible for the analysis. Using the X-tile software, which is a validated tool for outcome-based cut-point optimization [14–16], we selected the best cut-off values that divided patients into high-, medium- and low-risk groups. All these high-risk patients were classified into a risk group based on the formula and cut-off values. The BCSM rates were compared among the different risk groups, and the distribution of patients in different risk stratification groups between the cohorts (C1 and C2) was analyzed using the Pearson Chi-square test. The flexible parametric survival model was analyzed using the stpm2 packages in Stata (StataCorp, College Station, TX, USA, version 12). Other statistical analyses were performed using SPSS (version 20, IBM Software, IBM, Armonk, NY, USA). For all analyses, a two-sided p value lower than 0.05 indicated statistical significance.

3. Results

The SEER database identified 145,813 eligible patients for the analysis, with 69,726 patients in C1 and 76,087 patients in C2. Numerical difference was observed between the two cohorts with respect to basic characteristics, however, around 29% patients were grade 3, 31% were tumor size >2 cm, 34% were node positive and 81% were PR positive in both cohorts(Table 1). The median follow-up times were 154 (102–192) and 103 (88–122) months for patients in C1 and C2, respectively.

3.1. BCSM in the two cohorts

Fig. 2A shows the estimated continuous annual BCSM rates, which was reported per 1000 persons per year. The patterns of BCSM were similar between the cohorts, as the annual hazard accumulated through the first 4 years and peaked in the fourth year after diagnosis. After 4 years, the hazard rate plateaued and remained stable for a long period of time. Remarkably, the annual BCSM rates of C2 decreased throughout each yearly interval in all patients with ER-positive cancer among all of the subgroups (data