The Breast 37 (2018) 56–63

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Evaluation of the prognostic stage in the 8th edition of the American Joint Committee on Cancer in locally advanced breast cancer: An analysis based on SEER 18 database

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ARTICLE INFO

Article history:
Received 30 August 2017
Accepted 23 October 2017

Keywords:
Locally advanced breast cancer
TNM stage
Prognostic stage system
AJCC
Prognosis

ABSTRACT

Background: The new "prognostic stage" in the 8th edition of the American Joint Committee on Cancer (AJCC) incorporated important biologic factors such as estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER2), histologic grade and TNM stage into one system. The objective of this study was to evaluate the "prognostic stage" in locally advanced breast cancer (LABC) based on the Surveillance, Epidemiology, and End Results (SEER) 18 database.

Methods: 10053 LABCs diagnosed between 2010 and 2013 were enrolled. TNM stage was based on AJCC 7th edition. Comparisons of biologic factor proportions among stage changes were performed using Pearson's chi-square test. Breast cancer-specific survival (BCSS) and overall survival (OS) were estimated using the Kaplan-Meier method and log rank testing with pairwise comparisons between different stages was conducted. Cox models were fitted to assess the independent prognostic factors.

Results: The prognostic stage grouped LABC into six stages: IB-IIIC among which IB-IIIA had a relatively better survival. It reassigned 74% LABCs to a different tumor stage. 60.4% cases in grade III and 68.3% cases with triple negative breast cancer were upstaged while 57.1% cases with ER/PR dual positivity were down staged. It was an independent prognostic factor of LABC. There were statistically significant survival differences among stage IB-IIIA, IIIB and IIIC. Among each TNM stage, there were statistically significant survival differences among stage changes.

Conclusions: The prognostic stage provided accurate prognostic information for LABC compared with anatomic TNM stage. It will lead to accuracy in prognosis prediction and optimal treatment selection, and therefore, better outcomes.

1. Introduction

Breast cancer treatment should take into account both anatomic factors and biology characteristics [1]. The classic TNM staging system is based strictly on anatomic factors; it does not consider the prognostic impact of tumor biology. However, the advances in understanding breast cancer biology have resulted in the identification and validation of biologic markers of prognosis and treatment benefit [2].

Accordingly, the integration of both anatomic and biologic classification into one staging system was an unmet need. It helps to understand why patients who are staged similarly have significantly different outcomes based on tumor biology. Numerous studies proposed incorporating biologic factors into TNM stage. But most of them evaluated smaller groups of patients [3–7].

A new "prognostic stage" in the recently published eighth edition of the American Joint Committee on Cancer (AJCC) system included estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER2), histologic grade and conventional TNM variables into one staging system. Although it is only based on unpublished data from the National Cancer Data Base (NCDB), expert panel believes that additional data from other large populations of patients with full prognostic factor information and increasing longer follow-up will become available in the coming years [8].

Locally advanced breast cancer (LABC) is a great challenge in the treatment of breast cancer because a great proportion of patients will eventually relapse. Standard factors that traditionally defined

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https://doi.org/10.1016/j.breast.2017.10.011
0960-9776/

an advanced stage are potentially overruled by other biologic factors. Patients with advanced stage disease but favorable tumor biology had better clinical outcomes than those with stage I disease and unfavorable tumor biology [9]. LABC is commonly treated as a whole cohort. Anatomic TNM stage does not predict the clinical outcome precisely while incorporating biologic characteristics may refine the prognostic information and have as or more importance on selecting locoregional or systemic treatments, and as a result, lead to a better outcome.

The Surveillance, Epidemiology, and End Results (SEER) database is characterized with high quality and broad coverage, so we conducted a validation study based on SEER database to evaluate the new "prognostic stage" in LABC.

2. Materials and methods

2.1. Patient population

This retrospective study employed data derived from the National Cancer Institute's limited use SEER 18 registry databases that were released in November 2016. We identified female invasive ductal carcinoma (IDC) cases (with International Classification of Disease for Oncology, third edition (ICD-*O*-3) code of 8500) with AJCC IIIA-C stage (T3N1M0 excluded) diagnosed between 2010 and 2013. Patients with more than one primary cancer, having metastatic disease at diagnosis, diagnosed at death or autopsy only, age ≥80 years old, AJCC stage III NOS, unknown HER2 status or unknown histologic grade were excluded. TNM stage was based on a derived AJCC 7th edition. Prognostic stage for these cases was based on the prognostic stage system in the 8th edition of AJCC [8]. Poorly differentiated and anaplastic histological grades were considered grade III disease. Borderline ER or PR status was considered positive as ER/PR positivity was defined as >1% positive now.

We obtained permission to access the files of SEER program custom data with additional treatment fields such as radiation therapy and chemotherapy. The informed consent was not required because personal identifying information was not involved. This study was reviewed and approved by the Institutional Review Board of Obstetrics and Gynecology Hospital of Fudan University.

2.2. Statistical analysis

Comparisons of the proportions of biologic factors among the upstage or downstage classifications were performed using Pearson's chi-square test with Fisher's exact test. Follow-up cut-off was 31 December 2013. Overall survival (OS) was computed from the time of diagnosis of breast cancer to the time of death from any cause or last follow-up with patients still alive at last follow-up censored. Breast cancer-specific survival (BCSS) was computed from the time of diagnosis of breast cancer to the time of death from breast cancer with patients who died of other causes or still alive at last follow-up censored. Survival outcomes were estimated using the Kaplan-Meier product limit method and log rank testing with pairwise comparisons between different stages was conducted. Adjusted hazard ratios (HRs) with 95% confidence intervals were calculated using Cox proportional hazards model to assess the factors independently associated with survival. Two-sided $P < 0.05$ was considered statistically significant. All the statistical analysis was performed using SPSS 19.0 software package (SPSS, Chicago, IL, USA).

Table 1
Patient and tumor characteristics of LABC.

	cases	Percentage (%)
Age		
<50	3485	34.7
≥50	6568	65.3
Race		
White	7378	73.4
Black	1584	15.8
Asian or American Indian	1032	10.3
unknown	59	0.6
Marital status		
married	5346	53.2
unmarried	4228	42.1
unknown	479	4.8
Laterality		
left	5067	50.4
right	4984	49.6
unknown	2	0.0
Grade		
I	515	5.1
II	3511	34.9
III	6027	60.0
T stage		
T0	14	0.1
T1	1806	18.0
T2	4335	43.1
T3	1462	14.5
T4	2405	23.9
TX	31	0.3
N stage		
N0	423	4.2
N1	1058	10.5
N2	5710	56.8
N3	2862	28.5
Anatomic TNM Stage		
IIIA	5200	51.7
IIIB	1991	19.8
IIIC	2862	28.5
ER status		
negative	2879	28.6
positive	7170	71.3
unknown	4	0.0
PR status		
negative	4078	40.6
positive	5970	59.4
unknown	5	0.0
HER2		
negative	7477	74.4
positive	2576	25.6
Prognostic Stage		
IB	207	2.1
IIA	293	2.9
IIB	1805	18.0
IIIA	293	2.9
IIIB	3144	31.3
IIIC	4311	42.9
Lymph nodes removed		
none	738	7.3
<10 or biopsy	1967	19.6
≥10 or dissection	7310	72.7
unknown	38	0.4
Breast surgery		
no surgery	578	5.7
unknown	17	0.2
mastectomy	7039	70.0
BCS	2419	24.1
Radiation therapy		
no or unknown	3870	38.5
yes	6183	61.5
Chemotherapy		
no or unknown	1356	13.5
yes	8697	86.5