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Retrospective Prognostic Evaluation Using the 8th Edition *vs.* the 7th Edition of AJCC Staging System for Breast Cancer: A Single Institution Study of 3,140 Patients in Korea

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Abstract

Purpose: To evaluate whether the recently updated 8th edition of the American Joint Committee on Cancer (AJCC) staging systems represents better refinement of the 7th edition for breast cancer.

Methods: Data of 3,140 patients who were newly diagnosed with malignant breast cancer between January 2005 and December 2015 at a single institute were retrospectively reviewed. Invasive breast cancer was restaged according to the 8th edition of the AJCC staging system distributed on December 15th 2017. Five-year recurrence and survival rates were compared between the 7th edition and the 8th edition.

Results: According to the 7th edition and the 8th edition staging system, stage migration was observed in 947 (38.4%) patients. Of these, 214 (22.6%) patients showed upgraded stage while 733 (77.4%) patients showed downgraded stage with the 8th edition compared to those with the 7th edition. Using the 7th edition staging system, 5-year Recurrence Free Survival (RFS) rates for patients with stage IIB disease and stage IIIB were lower ($p<0.001$) than those of patients with stage IIIA and IIIC. Five-year Disease-Specific Survival (DSS) and Overall Survival (OS) rates for patients with stage IB disease were lower ($p<0.001$) than those of patients with stage IIA disease.

Conclusion: The recently updated 8th edition of AJCC staging system provides finer stratification of breast cancer with more accurate information about prognosis than the 7th edition staging system.

Keywords: Breast neoplasm; Recurrence; Survival; TNM staging system

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Introduction

Cancer staging systems provide information about the extent of disease that can be used to determine the best treatment for overcoming the cancer and help physicians estimate patient prognosis [1]. In addition, the staging system can be used to assess the efficacy of new treatment. Tumor, Lymph Node, and Metastasis (TNM) staging system published by the American Joint Committee on Cancer (AJCC) is the most commonly used cancer staging system worldwide [1]. The AJCC first announced TNM cancer staging system in 1977. Since then, it has released a revised edition every six to eight years. Changes in the staging system are periodically required to incorporate new diagnostic and therapeutic advances that affect risks of disease recurrence and patient survival [2]. This new edition of the AJCC Cancer Staging Manual was published in October 2016 and updated on December 15th, 2017. In the recently updated 8th edition of the AJCC Cancer staging system, the prognostic stage is subdivided into clinical prognostic stage and pathologic prognostic stage.

The aim of this study was to compare staging between the 7th edition and the recently updated 8th edition of the AJCC staging manual and evaluate whether the recently updated 8th AJCC classification for breast cancer could represent a better refinement of the 7th edition of the AJCC classification.

Methods and Patients

Patients and clinical data

In this single-center trial, data of a cohort of patients with biopsy proven malignant breast cancer who underwent surgical treatment and neoadjuvant/adjuvant treatment were reviewed retrospectively from a hospital's breast cancer enter database and patient's medical records. A total of 3,140 patients were newly diagnosed with malignant breast cancer in the Department of Surgery, Seoul St. Mary's Hospital, The Catholic University of Korea College of Medicine between January 2005 and December 2015. This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital (Approval number: KC18RCSI0163).

Patients with noninvasive carcinoma (e.g., ductal carcinoma *in situ*), distant metastasis at diagnosis, contralateral invasive breast cancer, previous or concomitant non-breast invasive malignancy, neoadjuvant treatment prior to operation, unknown Estrogen Receptor (ER)/Progesterone Receptor (PR)/Human Epidermal growth factor Receptor 2 (HER2) status, unknown Histologic Grade (HG), unknown any T or N stage, or follow-up loss after operation were excluded. Patients underwent surgical treatment and received adjuvant chemotherapy and/or endocrine therapy and/or radiation therapy according to standard protocols. Patients received clinical follow-ups every 6 months. Follow-up data were last updated on December 31st, 2017.

Recurrence-Free Survival (RFS) was defined as the time from the date of breast cancer operation to the date of the first recurrence including locoregional recurrence and distant recurrence. Disease-Specific Survival (DSS) was defined as the time from the date of breast cancer operation to the date of death due to breast cancer. Overall Survival (OS) was defined as the time from the date of breast cancer operation to the date of death.

Immunohistochemistry and assay methods

Immunohistochemistry (IHC) for ER (SP1, Prediluted; Roche Science, Mannheim, Germany), Progesterone Receptor (PR; 1E2, Prediluted; Roche), and Human Epidermal growth factor Receptor 2 (HER2; 4B5, Prediluted; Roche) was performed using whole tissue section slides and BenchMark ULTRA fully automated slide staining instrument (Ventana Medical Systems Inc., Tucson, AZ, USA). A positive ER and PR status was defined when an Allred Score (AS) was ≥ 3 or any staining for 1% of cells or more. IHC or fluorescence in situ hybridization was performed to evaluate HER2 status. A positive HER2 status was defined when an IHC score was 3+. If the IHC score was 2+, the sample was retested with single-probe silver in situ hybridization. Amplification ratio was defined as HER2 gene locus copy number relative to chromosome 17 centromere copy number and an amplification ratio of ≥ 2.0 was considered positive. HG was determined by tubule formation, nuclear pleomorphism, and mitotic count according to Scarff-Bloom-Richardson System-Nottingham Modification, assigning a value of 1 (favorable) to 3 (unfavorable) for each feature. Total score was obtained for all three categories. Combined scores of 3 to 5, 6 to 7, and 8 to 9 points were designated as grade 1, grade 2, and grade 3, respectively. All cancers were staged according to the 7th edition of AJCC staging system and the recently updated 8th edition of the AJCC pathological prognostic staging system in December 2017.

Statistical analysis

Clinical and pathological features were assessed using Student's t-test, Chi-square test, and Fisher's exact test. Cumulative RFS, DSS, and OS durations and probabilities were estimated using the Kaplan-Meier analysis. Survival curves were compared using log-rank test between survival rates. Hazard ratio and 95% confidence intervals were estimated for all variables. A two-sided p-value <0.05 was considered significant. All statistical analyses were performed with IBM SPSS software version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Of 3,140 patients, 2,464 were included in the analysis after excluding 676 patients who met the exclusion criteria. The mean age of these patients included was 51.03 ± 10.49 years. The median follow-up time was 59 months. Clinicopathologic characteristics for the entire cohort are summarized in Table 1. Five-year RFS and OS for the entire cohort were 90.0% and 96.1%, respectively.

Stage distribution and migration from AJCC 7th edition to the updated 8th edition staging system

The distribution of staging according to AJCC 7th edition and the updated 8th edition staging system is shown in Table 2. Using the 7th edition of the AJCC staging system, breast cancer stage was distributed as follows: Stage IA, n=1,292 (52.4%); Stage IB, n=47 (1.9%); Stage IIA, n=679 (27.6%); Stage IIB, n=233 (9.5%); Stage IIIA, n=124 (5.0%); Stage IIIB, n=2 (0.1%); and Stage IIIC, n=87 (3.5%) (Table 2). Using the 8th edition of AJCC, the distribution of breast cancer changed. On analysis, 1,517 of 2,464 patients (61.6%) had the same stage in both AJCC 7th and 8th staging systems. According to the 8th edition of AJCC staging system, stage migration was observed for 947 (38.4%) breast cancer patients: Upgraded, n=214 (22.6%); downgraded, n=733 (77.4%) (Table 2). By staging, stage IIB showed the greatest change except the stage IIIB (89.4%) (Table 2). All upgraded tumors were triple negative breast cancers (Table 3).

Five-year recurrence analysis according to the 7th AJCC edition and the updated 8th edition

According to the 7th edition of the AJCC staging system, 5-year RFS rate was 94.9% for stage IA, 92.5% for stage IB, 88.5% for stage IIA, 81.9% for stage IIB, 82.9% for stage IIIA, 50.0% for stage IIIB, and 63.6% for stage IIIC (p<0.001) (Figure 1). Five-year RFS rates for patients with stage IIB disease and stage IIIB were lower than those of patients with stage IIIA and IIIC (Figure 1A).

According to the 8th edition of AJCC staging system, the 5-year RFS rate was 94.9% for stage IA, 89.1% for stage IB, 84.2% for stage IIA, 78.3% for stage IIB, 73.7% for stage IIIA, 59.8% for stage IIIB, and 57.1% for stage IIIC (p<0.001) (Figure 1B). With the 8th edition of AJCC staging system, 5-year RFS rates were lower than those with the 7th edition at all stages. However, 5-year RFS rate was well distributed. It was decreased with increasing disease stage.

Five-year survival analysis according to the 7th edition and the updated 8th edition of AJCC staging system

The 5-year survival rate according to each stage per the 7th edition and 8th edition of AJCC staging system is shown in (Figure 2). Using the 7th edition of AJCC staging system, the 5-year DSS rate was 99.2% for stage IA, 93.5% for stage IB, 97.2% for stage IIA, 92.4% for stage IIB, 90.1% for stage IIIA, and 78.4% for stage IIIC (p<0.001) (Figure 2A). Patients (n=2) with stage IIIB disease had no death. The 5-year DSS rate for patients with stage IB disease was lower than that of

Table 1: Clinicopathologic characteristics of 2,464 enrolled patients.

Characteristics	Overall patients, n (%)
Age (years)	
<50	1142 (46.3)
≥ 50	1322 (53.7)
Breast operation	
Breast conservation	1490 (60.5)
Mastectomy	974 (39.5)
Axillary operation	
SLNB	1497 (60.8)
ALND	967 (39.2)
LVI	
No	1536 (62.3)
Yes	891 (36.2)
Unknown	37 (1.5)
Tumor stage	
1	1627 (66.0)
2	789 (32.0)
3	44 (1.8)
4	4 (0.2)
Nodal stage	
0	1756 (71.3)
1	445 (18.1)
2	114 (4.6)
3	87 (3.5)
Histologic grade	
G1	645 (26.2)
G2	1103 (44.8)
G3	716 (29.1)
ER	
Negative	680 (27.6)
Positive	1784 (72.4)
PR	
Negative	901 (36.6)
Positive	1563 (63.4)
HER2	
Negative	1869 (75.9)
Positive	595 (24.1)
Ki-67	
<20%	870 (35.3)
≥ 20%	1401 (56.9)
Unknown	193 (7.8)
Adjuvant chemotherapy	
No	789 (32.0)
Yes	1675 (68.0)
Adjuvant radiotherapy	
No	818 (33.2)
Yes	1646 (66.8)
Adjuvant endocrine therapy	
No	673 (27.3)
Yes	1791 (72.7)
Adjuvant trastuzumab therapy	
No	2264 (91.9)
Yes	200 (8.1)
Recurrence	
No	2219 (90.1)
Yes	245 (9.9)
Death	
No	2359 (95.7)
Yes	105 (4.3)

SLNB: Sentinel Lymph Node Biopsy; ALND: Axillary Lymph Node Dissection; LVI: Lymphovascular Invasion; ER: Estrogen Receptor; PR: Progesterone Receptor; HER2: Human Epidermal Growth Factor Receptor 2

patients with stage IIA disease.

The 5-year OS rate was 98.8% for stage IA, 93.5% for stage IB, 95.9% for stage IIA, 92.0% for stage IIB, 89.3% for stage IIIA, and 77.5% for stage IIIC ($p<0.001$) (Figure 3A). The 5-year OS rate for patients with stage IB disease was lower than that of patients with stage IIA disease.

Using the 8th edition of AJCC staging system, the 5-year DSS rate was 99.2% for stage IA, 96.3% for stage IB, 96.1% for stage IIA, 91.2% for stage IIB, 80.4% for stage IIIA, 77.0% for stage IIIB, and 74.5% for stage IIIC ($p<0.001$) (Figure 2B). The 5-year OS rate was 98.6% for stage IA, 96.0% for stage IB, 94.9% for stage IIA, 91.2% for stage IIB, 80.4% for stage IIIA, 75.3% for stage IIIB, and 71.5% for stage IIIC ($p<0.001$) (Figure 3B). With the 8th edition of AJCC staging system, 5-year DSS and OS rates were lower than those with the 7th edition at all stages. However, 5-year DSS and OS rates were well distributed. They were found to be decreased with increasing disease stage, similar to results found for 5-year RFS.

Discussion

The concept of cancer classification using anatomic extent of disease Tumor, Lymph Node, and Metastasis (TNM) was first introduced by Pierre Denoix in the 1940s and 1950s [1]. Based on this concept, the first edition of the AJCC TNM staging manual was published in 1977 [1,3]. Periodically updated TNM staging system provided by the AJCC has been widely used as a method for staging breast cancer patients. It is considered the most important reference in determining the prognosis of cancer and the best treatment [1,3]. With the publication of a study by Perou et al. [4], the importance of prognostic markers such as ER, PR, and HER2 has emerged [4-8]. ER, PR, and HER2 have been considered as predictive and prognostic markers. Several studies have assessed risk factor profiles of tumor subtypes [8-12]. Finally, the 12th St Gallen International Breast Cancer Conference expert panel adopted a new approach to classify breast cancer based on recognition of intrinsic biological subtypes [7,8,13]. In October 2016, the 8th edition of the new AJCC TNM staging manual applied this concept. There are several changes in the 8th edition of breast cancer staging system compared to the 7th edition [1,3,14].

A major change in breast cancer staging is that anatomic staging of cancer defined by T, N, and M categories is intended for use in settings around the world where biomarker analysis is unavailable.

Stage	7th edition, *n* (%)	8th edition, *n* (%)
IA	1292(52.4)	1546(62.7)
IB	47(1.9)	366(14.9)
IIA	679(27.6)	296(12.0)
IIB	233(9.5)	78(3.2)
IIIA	124(5.0)	108(4.4)
IIIB	2(0.1)	45(1.8)
IIIC	87(3.5)	25(1.0)

AJCC: American Joint Committee on Cancer

Table 2: The number of patients migrated in the updated 8th edition of the AJCC staging system for breast cancer compared to that with the 7th edition.

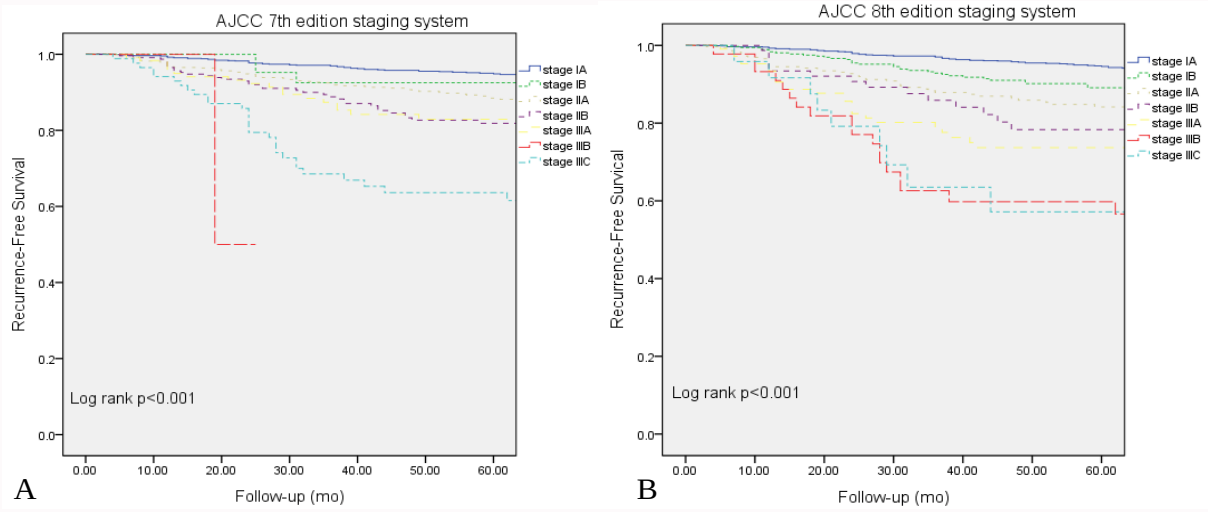

Figure 1: Five-year recurrence-free survival in the 7th edition AJCC staging system (A) and in 8th edition of the AJCC staging system (B).

When biomarkers are available, cancers should be staged using the prognostic staging system, including anatomic T, N, and M plus HG of cancer and the status of biomarkers such as ER, PR, and HER2 [1,14]. A combination of traditional anatomic information reflecting tumor burden and biological information reflecting intrinsic characteristics of tumor can provide more rational and diversified basis for physicians to understand features of a specific tumor and make more personalized treatment decision.

In the recently updated 8th edition of AJCC Cancer staging system published on December 15th, 2017, the prognostic stage was subdivided into clinical prognostic stage and pathologic prognostic stage. Clinical prognostic stage can be used for all breast cancer for clinical classification and staging. Genomic profile information is not included. Pathologic prognostic stage can be applied to breast cancer treated with operation as the initial treatment prior to systemic or radiation treatment [15]. It includes all information used for clinical staging plus finding at surgery and pathologic findings from surgical resection.

This study compared results of the updated 8th pathologic prognostic staging system with results of the previous 7th staging system to determine which staging system might be more useful. Stage migration was observed in 947 (38.4%) breast cancer patients, including 214 (22.6%) breast cancers that were upgraded and 733 (77.4%) that were downgraded according to the updated 8th edition staging system. The most breast cancer with stage IIB in the 7th edition had migration to other stages (89.4%). Other studies using the 8th staging system *vs.* the 7th edition have suggested that the rate of stage migration is higher than 50% [13,16-18].

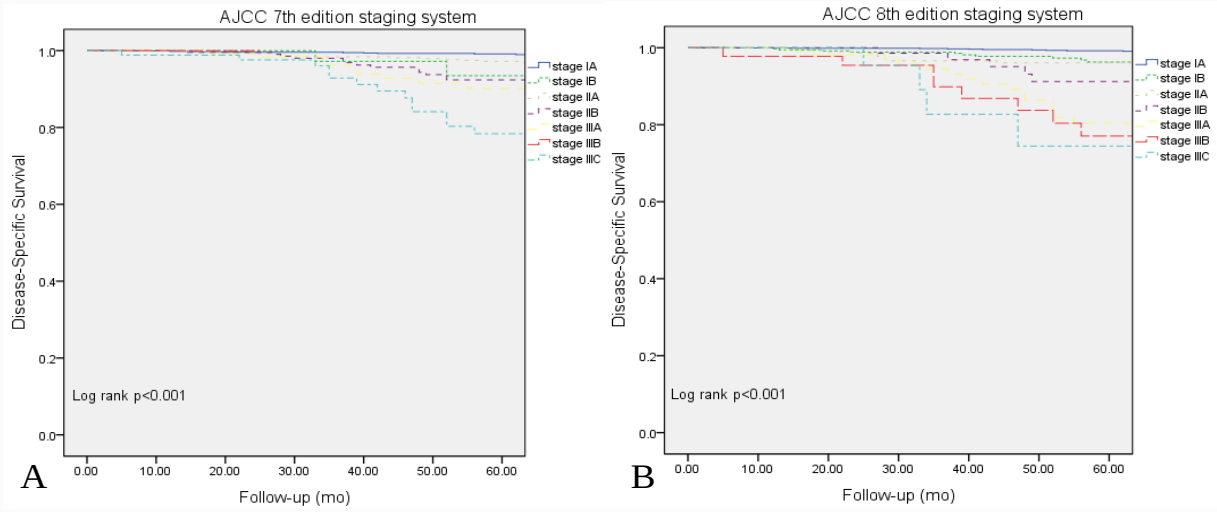

Figure 2: Five-year disease specific survival with the 7th AJCC edition staging system (A) and the 8th edition of AJCC staging system (B).

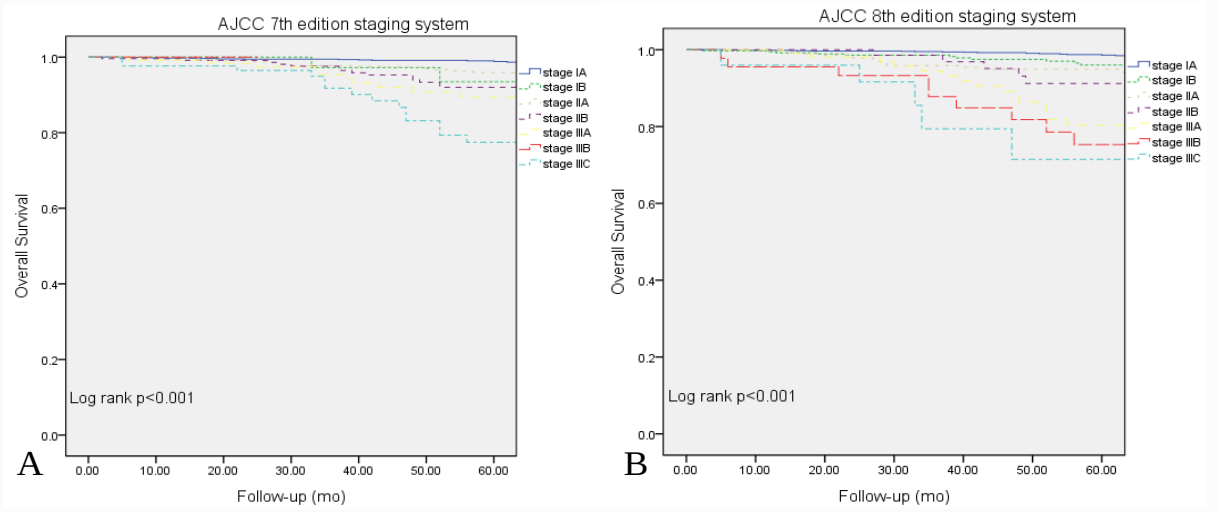

Figure 3: Five-year overall survival in the 7th edition of AJCC staging system (A) and the 8th edition of AJCC staging system (B).

Table 3: Association between molecular subtype and stage migration.

Molecular subtype	Downgraded tumor, n (%)	Upgraded tumor, n (%)	p
Luminal A	204 (29.8)	0	
Luminal B (HER2 negative)	334 (48.8)	0	
Luminal B (HER2 positive)	126 (18.4)	0	
HER2	19 (2.8)	0	
TNBC	1 (0.1)	198	

*Statistical analysis was performed on breast cancer except for unknown Ki-67

According to the 7th edition of AJCC staging system, the 5-year RFS rate was 81.9% for stage IIB, 82.9% for stage IIIA, 50.0% for stage IIIB, and 63.6% for stage IIIC (p<0.001). High stage showed rather high recurrence rate. However, when they were reclassified by the updated 8th edition, the 5-year RFS rate was well distributed. It was found to be decreased with increasing disease stage. The 5-year DSS rate was 93.5% for stage IB and 97.2% for stage IIA. The 5-year OS rate was 93.5% for stage IB and 95.9% for stage IIA in the 7th edition staging system (p<0.001). Like the 5-year RFS, high stage had rather high recurrence rate, especially between stage IB and stage IIA. According to the updated 8th edition, 5-year DSS and 5-year OS were well represented by stage. To the best of our knowledge, this is the first study shows that discrimination of recurrence and survival rate between each stage is clearer using the updated 8th edition staging system of AJCC than that with the 7th edition.

This study had some limitations. First, results of genomic profile were not included in our study. Although genomic profiles may provide good information in determining appropriate treatment, they are not required to assign pathologic prognostic stage. However, this is the first study that identifies differences in 5-year recurrence and survival rates between the 7th edition and the recently updated 8th

editions of the AJCC staging system for breast cancer. We used single-institutional data and obtained results based on coherent treatment protocols. Standardized measurements of IHC and pathologic results were performed or obtained by a single pathologist at a single institution. Results of our study might also be reliable because only patients with accurate information on tumor size, lymph node status, ER, PR, HER, and HG required for staging of the 8th edition is included while patients follow-up loss after operation are excluded.

Conclusion

The recently updated 8th edition of the AJCC staging system provides finer stratification of breast cancer with more accurate information about prognosis than the 7th edition staging system. It is especially useful when trying to predict recurrent prognosis for stage IIB and IIIA and the survival prognosis for stage IB and IIA.

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