



Historical progress of the 8th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual in patients with breast cancer

Yoshimasa Kosaka, Hiroshi Nishimiya, Mariko Kikuchi, Mina Waraya, Hiroshi Katoh, Norihiko Sengoku

Department of Breast and Endocrine Surgery, Kitasato University School of Medicine, Kanagawa, Japan

Correspondence to: Yoshimasa Kosaka. Department of Breast and Endocrine Surgery, Kitasato University School of Medicine, 1-15-1, Kitasato, Minami-ku, Sagami-hara, Kanagawa, 252-0374, Japan. Email: y-kosaka@med.kitasato-u.ac.jp.

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Breast cancer is the most frequently diagnosed cancer and second leading cause of cancer death in countries around the world (1). Anatomic information, including information about the primary tumor (T), lymph node metastasis (N), and distant metastasis (M), has long been recognized to be indicative of cancer prognosis. Since this Tumor-Node-Metastasis (TNM) classification was defined in the 1st edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, most clinicians have used this manual to predict prognosis and select treatment (2). Along with an improved understanding of cancer biology, multiple agents that target specific proteins have been developed in the past several decades. For breast cancer in particular, many agents, including hormone therapies and anti-human epidermal growth factor receptor 2 (HER2) and other targeted agents have been introduced. Therefore, since anatomic factors do not necessarily reflect tumor biology, biological information is also important for predicting prognosis. In fact, significant differences in treatment response and long-term outcomes have been observed between breast cancer biologic subtypes (3-5).

The AJCC released the 8th edition of their Cancer Staging Manual in 2017 (6,7). The new edition includes the addition of four biologic factors—tumor grade, estrogen receptor (ER) expression, progesterone receptor (PR) expression, and HER2 expression—to the anatomic cancer staging manual. Briefly, the anatomic stage groups are similar to the stage groups of the 7th edition, in which patients with triple-negative or grade 3 diseases were

upstaged in the prognostic stage groups. This manual provides a reasonable reference for clinical decision-making.

The aim of the analysis conducted by Kim *et al.* was to validate survival rates by comparing the 7th and 8th editions of the AJCC Cancer Staging Manual using data from the Korean Breast Cancer Society (KBSC) (8). The AJCC Cancer Staging Manual is recommended for patients in the United States, because the prognostic stages were developed from 238,265 patients in the National Cancer Database treated between 2010 and 2011 for whom complete data were available, including the TNM, tumor grade, ER, PR, and HER2 status. Although Weiss *et al.* reported the results of a validation study conducted in the United States based on data from the California Cancer Registry (CCR) (9), no studies have been performed in different population databases, particularly the Asian race. Kim *et al.* collected data from 24,014 patients with invasive breast cancer who underwent surgery between 2009 and 2012 in Korea. This large number of breast cancer patients is noteworthy. Although some data are available from 113,485 patients in the KBSC from 1990 to 2012, biological status was only accurately measured beginning in 2009. Despite the large amount of excluded data, their included data appear to be robust.

In the study by Kim *et al.*, 26.1% of patients were upstage and 19.4% patients were downstage with the 8th edition compared to the 7th edition. Disease-free survival (DFS) and overall survival (OS) decreased by clinical and pathological prognostic stage group from stage IA to IIIC. However, by anatomic stage group, patients with stage IIA

disease had better prognosis than those with stage IB disease, and patients with stage IIIC disease had better prognosis than those with stage IIIB disease. The Harrell concordance index (C-index) for OS and DFS was higher for clinical prognostic stage groups (0.770 and 0.851, respectively) and pathological prognostic stage groups (0.766 and 0.874, respectively) than for anatomic stage groups (0.732 and 0.828, respectively). The hazard ratios for DFS and OS increased by stage, from IA to IIIC, for clinical prognostic stage groups but not for anatomic stage groups (8). Weiss *et al.* conducted a survival analysis using data from the large population-based CCR (n=50,982) (9). The C-index of prognostic stage groups (0.8426) was higher than that of anatomic stage groups (0.8097). Furthermore, the hazard ratio for disease-specific survival was similar to that obtained by Kim *et al.*

According to the definition of the 2007 St. Gallen Breast Cancer Consensus Conference, breast cancer is classified into four subtypes: luminal-A (ER- and/or PR-positive, HER2-negative), luminal-B (ER- and/or PR-positive, HER2-positive), HER2-positive (ER- and PR-negative, HER2-positive), and triple-negative (ER-, PR-, and HER2-negative) (10). This classification has been used to formulate guidelines for breast cancer therapy, including the use of systemic adjuvant therapies by subtype and risk category. In 2009, the indication for endocrine therapy changed from >10% staining to presence of any ER staining in the tumor (11). In 2011, the St. Gallen Breast Cancer Consensus Conference suggested that the Ki67 index should also be considered, resulting in the following five subtypes: luminal-A (ER- and/or PR-positive, HER2-positive, and low Ki67), luminal-B HER2-negative [ER- and/or PR-positive, HER2-positive, and high Ki67 (>15%)], luminal-B HER2-enriched (ER- and/or PR-positive, HER2-positive), HER2-positive, and triple-negative (12). With respect to the definition of HER2-positive disease, the HER2 testing guidelines were updated in 2013 by the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) (13). These changes greatly impacted oncologists and required treatment strategies to be revised. Moreover, the most dramatic change was the indication for anti-HER2 therapy. Since 2001, trastuzumab has been used to treat metastatic HER2-positive disease (14). In 2008, the FDA approved trastuzumab for HER2-positive patients as adjuvant therapy based on the Herceptin Adjuvant (HERA) trial (15). As a result, the prognosis of breast cancer patients with HER2-positive disease improved (16). However, whether patients with HER2-positive disease received anti-HER2 therapy has

influenced the results of retrospective studies. The results of Kim *et al.* revealed that the new prognostic stages included in the 8th edition of the AJCC Cancer Staging Manual also provide accurate prognostic information for other races.

Another significant change in the 8th edition of the AJCC Cancer Staging Manual is inclusion of a multigene panel using a 21-gene assay (OncotypeDx[®]) in specific situations. Patients with T1-2N0M0, ER-positive, HER2-negative disease and an OncotypeDx[®] recurrence score <11 are considered to have pathologic prognostic stage IA disease. Although based on a large database from the Trial Assigning Individualized Options for Treatment (TAILORx) trial (17), multigene assays, including OncotypeDx, have not been approved by government health insurance systems in some countries. Additional studies are needed to validate multigene assays in the countries.

The information provided in the AJCC Cancer Staging Manual has limitations in clinical settings, including assessment of Ki67 expression level, efficacy of neoadjuvant systemic therapy, and use of new agents for patients with metastatic disease (e.g., CDK4/6 inhibitors, PARP inhibitors, and immunotherapy). In the study by Kim *et al.*, patients with stage IIIC, primarily triple-negative, breast cancer experienced a poor prognosis. Recently, the anti-PD-L1 agent atezolizumab prolonged progression-free survival (PFS) in patients with metastatic triple-negative breast cancer (TNBC) (18). Additional immunotherapies are expected to demonstrate efficacy in patients with aggressive TNBC. Moreover, a new era of precision medicine using next-generation sequencing for breast cancer has arrived. The new AJCC Cancer Staging Manual is suitable for assessing accurate prognostic information. However, it will be need to continue be updated and validated in the future.

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