Review Article (Invited)

TNM classification of malignant tumors
(Breast Cancer Study Group)

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Abstract
The eighth editions of the primary tumor, lymph node and metastasis classifications for breast cancer issued by the American Joint Commission of Cancer and the Union for International Cancer Control were revised in 2017. The major change made by the American Joint Commission of Cancer is to incorporate biological factors such as estrogen and progesterone receptor, human epidermal growth factor receptor 2, histological grade and multigene prognostic assays, into the staging system. Tumor biomarkers and low recurrence scores confirmed by multigene prognostic assays change the staging. Minor changes are to add the post-neoadjuvant therapy clinical and pathological classification and to define the size of tumor, lymph node and metastasis components more precisely. Little has changed in the Union for International Cancer Control. We have identified key points of change in both eighth editions of the tumor, lymph node and metastasis classifications and we discuss possible problems which may arise when they are adopted in Japanese practice, as well as future directions.

Key words: breast cancer, TNM classification, eighth edition, AJCC, UICC

Introduction
The primary tumor, lymph node and metastasis (TNM) classification staging system was first published in 1959 by the American Joint Commission of Cancer (AJCC) (1). Since then, it has been regularly updated, with the seventh edition published in 2009 (2). A new version, the eighth edition of the TNM classification, was revised and published in 2017 (1). The TNM categories are determined and disease stage is defined at the time of diagnosis. The clinical stage is assigned based on physical examination and imaging studies, while the pathological stage is assigned after surgery. The aim of the staging is to predict the patient’s prognosis and to determine a treatment plan based on this. In this review we describe the major changes to the eighth editions of the staging systems published by the AJCC (AJCC-TNM) (1) and the Union for International Cancer Control (UICC) (UICC-TNM) (3). First, we summarize the changes to these two staging systems and secondly, we discuss problems which may arise when they are adopted in Japanese practice and consider future directions.

Points of change in the eighth edition
AJCC-TNM

Major changes
The most radical change is the incorporation of biological factors into the traditional anatomical staging as the prognostic stage group. This incorporates biological factors, such as expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2), histological grade, and multigene prognostic assays into the staging system, although the tumor staging system remains based on TNM anatomical factors. The prognostic stage gives more precise information with respect to survival than the anatomical stage alone, and this model was based on analysis of 238,265 patients using the National Cancer Database (1). In Table 1, we show some examples of the effect of biomarkers with regard to the change of staging. For example, a patient may be categorized as IA by anatomical TNM, but if she has a triple-negative tumor, her prognostic stage is IIA. Similarly, if a patient of...
stage IIIA by anatomical TNM has a grade one tumor that is HER2-positive and ER/PR-positive, her prognostic stage is IB. If the score from a mutigene panel assay using Oncotype DX® is less than 11, for a patient with an ER-positive and HER2-negative tumor with an anatomical TNM score of IIA, the new system indicates IA of prognostic stage regardless of grade or PR.

Gene expression profiling has identified several intranuclear molecular subtypes of breast cancer (4,5). Clinopathological examinations for ER, PR and HER2 are used as surrogates for gene expression profiling and are measured using immunohistochemical methods or in situ hybridization (6). These biomarkers have been evaluated in prospective trials and can provide sufficient prognostic information. The value of mutigene profiling assays has also been studied (7–9). Finally, prognostic knowledge has been added, because both tumor biomarkers identified by pathological examination and the score of multigene profiling assays could alter prognosis and stage (10). With respect to the detail in multiparameter prognostic assays, Oncotype Dx®, Mammaprint®, EndoPredict®, PAM50® and Breast Cancer Index were also included in the eighth version; among them, Oncotype Dx® is the only one rated the AJCC level of evidence I, whereas the others are the AJCC level of evidence II. In the Phase III study TAILORx trial using Oncotype Dx®, the results of a single arm cohort of patients with ER-positive, HER2-negative, node-negative breast cancer who had a favorable gene expression score showed that they had a very low rate of recurrence with endocrine therapy alone (8). Later, in the randomized cohort arms of patients who had a mid-range recurrence score, adjuvant endocrine therapy and chemo-endocrine therapy were found to have similar efficacy (9).

**Minor changes**

Some minor points have also been changed.

**Lobular carcinoma in situ (LCIS)** LCIS has been removed from the eighth edition because it is not a malignancy, but it is a risk factor (11). It is no longer included in the pathologic tumor in situ (pTis) category. Instead, LCIS is treated as a benign category with an associated risk of carcinoma in the future. There is one form of LCIS, known as pleomorphic or high-grade LCIS, which has features that partially overlap those of ductal carcinoma in situ (DCIS) and this form is treated similarly to DCIS.

**Definition of primary tumor (T)** The seventh edition included a rule for rounding tumor size to the nearest millimeter, but in the eighth edition, the maximum invasive tumor size is used as a more reliable indicator of tumor volume. When synchronous tumors are present, the size of the largest tumor focus should be used for T classification; the smaller tumor sizes need not be measured or added to the maximum tumor size. The T categorization of multiple synchronous tumors is clarified. In the eighth edition, if a tumor is incidentally identified microscopically separate from the main lesion, it would be permissible to use the (m) modifier, particularly when the tumors have different histological or prognostic receptor status. The eighth edition has also added a clear definition indicating that satellite tumor nodules in the skin must be separate from the primary tumor and macroscopically identified for the tumor to be categorized as T4b. Skin and dermal tumor satellite nodules identified only on microscopic examination and in the absence of epidermal ulceration or skin edema (clinical peau d’orange) do not qualify as T4b. Such tumors should be categorized based on tumor size.

**Definition of regional lymph node (N)** In the eighth edition, no major changes have been made to N classification, but the criteria for pathological measurement of lymph node metastases have been clearly defined. The dimensions of any area containing several or multiple tumor deposits are not used to determine pathological N (pN) category, but the largest contiguous tumor deposit is used for pN. This is the same principle as used for T classification, described above. The eighth version also clarified that cNX is not a valid category unless the lymph node basin has been removed and cannot be examined by imaging or clinical examination; a cN0 category is to be assigned when any evaluation of the lymph nodes is possible, and physical examination or imaging examination is negative.

**Definition of distant metastasis (M)** In the eighth edition, no changes have been made to M classification. All cases should be categorized as either cM0 or cM1; pM0 is not a valid category, although when metastatic disease is confirmed by biopsy, the pM1 category is used. A classification of cM0 (+) is used if there is no clinical or imaging evidence of distant disease, but there is molecular or microscopic evidence of circulating tumor cells or disseminated tumor cell deposits no larger than 0.2 mm in the bone marrow or in other non-regional lymph nodes.

**Post-neoadjuvant therapy classification (ypTNM)** The eighth edition includes the pathological T category (ypT) for post-neoadjuvant therapy. The category ypT is based on the largest focus of residual tumor. Treatment-related fibrosis adjacent to residual invasive carcinoma is not included in the ypT maximum dimension. When multiple foci of residual tumor are present, the (m) modifier is included. The finding of residual DCIS after neoadjuvant therapy is classified as ypTis. The largest focus of residual tumor in the lymph nodes, if present, is used for ypN categorization. Treatment-related fibrosis adjacent to residual lymph node tumor deposits is not included in the ypN dimension and classification. The M category for patients treated with neoadjuvant therapy is the category assigned at the pretreatment clinical stage, prior to initiation of neoadjuvant therapy. If a patient was designated as having detectable distant metastases (M1) before chemotherapy, the patient will be designated as M1 throughout.

### Table 1. The example of eighth edition of AJCC prognostic stage (1)

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
<th>IA</th>
<th>IIA</th>
<th>1</th>
<th>2 N0 M0 IA, IIA 1</th>
<th>1–3</th>
<th>Negative</th>
<th>Negative</th>
<th>Negative</th>
<th>Negative</th>
<th>IIA</th>
<th>IB</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 N0 M0</td>
<td>IA</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>IB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 N2 M0</td>
<td>IIIA</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>IB</td>
<td></td>
<td></td>
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<tr>
<td>MutiGene Panel-Oncotype Dx® Recurrence score less than 11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Negative</td>
<td>Positive</td>
<td>Any</td>
<td>IA</td>
<td></td>
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</tr>
</tbody>
</table>
UIICC-TNM

Little has changed in the TNM categories of the UIICC-TNM (3). There is one small difference regarding the pN1b and pN1c categories. In the eighth edition, biological factors are not incorporated in the UIICC-TNM classification of malignant tumors, although ‘Prognostic Factor Grid’ section was adopted. Whereas the anatomical extent of disease as categorized by TNM is a powerful prognostic indicator, it has been recognized that many factors have a significant impact on predicting outcomes. In the edition, the term ‘stage’ has been used as defining the anatomical extent of disease while ‘prognostic group’ for classifications that incorporate other prognostic factors. Prognostic factors for breast cancer can be classified to tumor related profile (ER, HER2, histological grade, involved nodes, tumor size, lymphatic or vascular invasion and surgical margin status), host related profile (age and menopausal status) and environment related profile (prior radiation).

The ‘Essential TNM’ section was also adopted from the eighth edition of the UIICC-TNM to facilitate the collection of stage data for cancer surveillance in low- and middle-income countries when complete information was not available.

Discussion

Above, we have highlighted the points of change in the eighth edition of the TNM classification and difference between the AJCC and UIICC eighth versions. Here, we discuss problems and future directions related to their application in Japan. The purpose of the TNM staging system is to predict the prognosis, in other words ‘base-line risk’ of breast cancer at diagnosis and after surgery. The main utility of staging is to predict subsequent recurrence in patients who do not receive systemic therapy and to guide whether the patient should or should not receive adjuvant chemotherapy or endocrine therapy or anti-HER2 therapy. However, there are few data regarding patients who have not received any treatment because standard systemic therapies have been applied for three decades in almost all patients with Stages I-III. Data from patients after curative surgery with no systemic treatment are needed in order to precisely predict prognosis. As for the incorporation of biological features in the eighth edition of the AJCC-TNM, this is reasonable for predicting prognosis because treatment decisions are mainly based on the biological characteristics of the primary tumor rather than the extent of disease. However, there are some problems. The prognostic stage is mainly based on data from patients who underwent standard chemotherapy, hormonal therapy and anti-HER2 therapy, if indicated. Then, there are differences with regard to the risk of recurrence between patients who received standard therapy according to the subtype and patients who did not receive any treatment. Thus, for example, elderly patients who cannot receive standard chemotherapy because of their frail condition would have a different prognosis, even if the prognostic stage was the same. With regard to the availability of a multigene expression assay, the worldwide situation has become more complex. Finances are also problematic in some countries. In Japan, multigene prognostic assays are not covered by public insurance (as of August 2018), although the value of multigene panels has been incorporated into national guidelines and recommendations for treatment (12,13). As a result, in Japan we are encouraged to use only biological factors identified by immunohistochemical staining, combined with the anatomical stage, although a new gene expression profiling assay with a DNA microarray—the ‘95-gene classifier’—has been developed in Japan (14). We believe that validation in a larger cohort is needed before the risk profile using these biological factors can be incorporated into AJCC-TNM staging.

With regard to multigene panels, in low-risk patients, defined according to the 21-gene recurrence assay, Oncotype Dx®, and who received endocrine therapy alone without chemotherapy, downstaging to Stage I based on biology is supported by the low rate of recurrence (8). However multigene panels would be incorporated into the staging system only for node-negative, ER-positive and HER2-negative subtypes. The National Comprehensive Cancer Network (NCCN) recommends that the use of multigene panels such as the Oncotype Dx® to estimate recurrence score may provide prognostic and predictive information in addition to anatomical staging and ER, PR and HER2 status, but other prognostic multigene assays have not yet been validated (13). As for other assays, a prospective randomized study using a 70-gene signature assay (MammaPrint®) showed that women at high risk of metastases according to clinical factors, but at low genomic risk, who did not receive systemic adjuvant chemotherapy had a high rate of 5 year survival (15). As a perception, the accumulation of the validation data for other multigene profiling assays is needed to modify the new staging system for breast cancer and future modifications based on biological data with the results of prospective studies will be needed. The incorporation of biomarkers and multigene profiling assays into the eighth edition of the AJCC staging system allows for more precise staging that reflects the prognosis.

There are some differences between the AJCC-TNM and UIICC-TNM guidelines as reported above, although these two sources should reflect the same staging principles and definitions. The UIICC staging system has not incorporated biological staging because the availability of tests and ability to evaluate biological features differ among different countries around the world (10). In Japan, the newest edition of general rules of breast cancer edited by the Japanese Breast Cancer Society has also not incorporated biological staging (16), like the UIICC-TNM, although problems with biological features are discussed by the committee of the society. The systems of prognostic staging require continuous updating based on reports of additional outcomes of prospectively-designed studies. These will be incorporated into the new edition of the ‘General rules for clinical and pathological recording of breast cancer’, produced by the Japanese Breast Cancer Society in the future, if biological markers and genomic assays are standardized across the world, and survival can be predicted more precisely. Continuous discussion is needed regarding whether we should use the UIICC-TNM, or the AJCC-TNM with its more detailed prognostic stages. We consider that the traditional anatomical staging is also mandatory, because anatomical TNM staging has been changing and progressing for decades, therefore, it can still be used to refer to previous TNM staging versions for comparison using historical data. The update of staging version for both anatomical and prognostic TNM will depend on the availability and validity of prognostic and predictive factors using biological markers and genomic assays and in future will enable more precise prediction of survival at diagnosis and post-surgery.

Conclusions

We summarized the changed points of the eighth editions of the AJCC-TNM and UIICC-TNM staging systems. The new version of AJCC-TNM staging provides a prognostic classification based on both traditional anatomical factors and newly added biological factors. Continuous discussion is needed to ascertain how best we should deal with the AJCC-TNM with its more detailed prognostic stages.
Conflict of interest statement

The authors state that there is no conflict of interest.

References


