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The Recently Developed TNM-Based Breast Cancer Staging

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Abstract

This study details the modifications made to the Tumor–Node–Metastasis (TNM)-based staging of breast tumors by the most recent, eighth editions of the pertinent publications from the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC). After providing some background information on TNM's status as the standard language for cancer staging and associated activities, such as cancer treatment and registration, it summarizes the changes and goes over some key points that pathologists should be aware of. It also lists and discusses the differences between the publications and diagnostic procedures that are based on them. Although not included in the UICC TNM classification of malignant tumors, a part is devoted to the prognostic stages of breast carcinomas that were presented in the AJCC Cancer Staging Manual. The review concludes with some final thoughts that raise the possibility of a loss of the common staging language. These issues include multifocal tumors, larger lymph node metastases identified by molecular methods, and the heterogeneous prognosis of M1-defined stage IV disease, all of which the authors believe are not adequately covered by TNM.

Keywords Breast cancer. TNM staging

Introduction

A communication channel, a communicative system (i.e., a common language), a communicator (e.g., the speaker or author), and a recipient (the receiver) are all necessary for an efficient communication. Many malignancies can be traced to follow this sequential path, and it has long been known that the prognosis for local (alone), regional (with metastasis to neighboring lymph nodes), and metastatic (with hematogenous dissemination to distant organs) tumors worsens accordingly. The staging of carcinomas, including breast malignancies, is now based on this. Based on Pierre Denoix's work from the 1940s, the Tumor-NodeMetastasis (TNM) method has been used globally from its inception to characterize the anatomic extent of cancer and identify its stage; as such, it is the common language of tumor staging. Six primary goals are identified by this common language: (1) to help clinicians plan treatments; (2) to provide some prognostic indications; (3) to help evaluate and compare treatment outcomes; (4) to facilitate information sharing

amongst various treatment facilities; (5) to support ongoing research on malignant tumors; and (6) to support cancer control initiatives [1].

The term "TNM" suggests that the prognosis of the tumor is reflected in the characteristics of the primary tumor (usually its size, but also other aspects like its relationship to surrounding structures), the regional lymph nodes (usually the number and/or location of involved nodes, but also other aspects like the size of the nodal involvement or the presence of extracapsular extension), and whether distant metastases are present or not. Additionally, it has been acknowledged that stage does not accurately represent the tumor's biology, which was first determined by its grade. While grade is a useful indicator of tumor aggressiveness, it is yet insufficient on its own to predict response to particular treatments and represent prognosis. Therefore, to better define what may be expected from a particular cancer or a group of related malignancies, disease stage components must be combined with a variety of other characteristics.

The TNM system is constantly changing, just like other languages, and the eighth version was released at the end of 2016. Several new parameters are included in the updated edition. In light of breast cancer and breast pathology, this review attempts to discuss the changes made to the eighth edition. Throughout the text, TNM will be used to refer to the specified edition, followed by the appropriate edition number. Readers should refer to the original articles for definitions of each category and stage, as the review will not replicate them [1, 2].

The staging books for TNM

There are two primary sources for the TNM-based staging system for oncological illnesses. The TNM Classification of Malignant Tumors (UICC-TNM) is one that is published by the Union for International Cancer Control (Union Internationale Contre le Cancer; UICC) [1]. Experts from the TNM Core Committee, Evaluation Committee, Prognostic Factors Committee, 21 National and Regional Committees, and Expert Panels have revised the book's content [3].The other source is the American Joint Committee on Cancer's (AJCC; AJCC-TNM) AJCC Cancer Staging Manual [2], which was revised based on input from seven AJCC Cores, 18 expert panels, authors from 22 countries across six continents, and—most importantly—defined and mentioned levels of evidence [2, 4]. The first one discusses breast cancer on 8/272 pages (1.9 × 12.8 × 19.2 cm), while the second one devotes 40/1024 pages (5.1 × 21.6 × 27.9 cm) to the topic. Theoretically, the staging concepts and terminology in these two sources ought to be identical. Regretfully, over time, there have been both convergences and divergences. For instance, various interpretations of what defines isolated tumor cells (a node-negative staging category) or micrometastasis (a node-positive status) have resulted from phrasing differences between the 6th and 7th editions [5–7]. The UICC Help desk still displays the following statement in spite of the need for a common language: Unfortunately, certain discrepancies have happened between the AJCC and UICC TNM classifications, even though there should not be any [8]. The timing of the new TNM-based staging's introduction is the first significant difference. While the AJCC-related resources explain why this should be applied at a national level starting in January 2018[9], the UICC Help desk claims that the new TNM is effective as of January 2017 [8].Since the books did not come out

until December 2016 and were not available until early 2017, it seems sense to postpone the launch. It is advised to include the edition of the TNM utilized in order to get around implementation issues [8]. Although some more or less permissive codifications of proper usage are occasionally developed, language growth is often a gradual process during which variations occur. One could compare the new TNM-related book editions to these linguistic codifications. According to the recommendations, a correct TNM classification ought to resemble this: T1miN0M0 (TNM7). This may be helpful at any time, even though the recommendation to mention the edition is intended to prevent confusion in 2017, when some users may be running TNM7 and others TNM8. For instance, the pN1a (TNM5) category is not identical to the pN1a (TNM6–8) category since it is changed to pN1mi from TNM6 on.

Highlights, modifications, and variations to the conventional stage defining categories

An eight-page list of errata currently exists, however it excludes errors pertaining to the breast cancer chapter [10]. There has been little to no change in the TNM categories of UICC-TNM. There is only one minor variation in the terminology of the pN1b and pN1c categories between UICC-TNM7 [11] and UICC-TNM8 [1]. The AJCC-TNM8 [2] and the UICC-TNM8 [1] or AJCC-TNM7 [12] have one significant difference in the categories, however. This includes the exclusion of lobular carcinoma in situ (LCIS) and its pTis (AJCC-TNM8) variations. Its malignant nature is not supported by level I evidence, and there is also inadequate evidence to support the idea that its variations are distinct. Thus, the term "benevolent entity" refers to LCIS. Theoretically, this also has an impact on the rare pTis (Paget) category, which is characterized by the presence of Paget's disease along with the exclusion of invasive or in situ cancer. Out of 114 patients in one of the biggest single-institution collections of Paget's illness, only 7 had no associated aggressive or in situ cancer [13]. It is true that ductal carcinoma in situ (DCIS) is typically viewed differently than lobular neoplasia, which includes both atypical lobular hyperplasia and LCIS. Its extent, for instance, cannot be quantified (Bis unreliable, unneeded, and unhelpful^), or it is classified as B3 on core needle biopsies [14], and when it is present in the inked margin, it is not reported as margin involvement. Nonetheless, there are frequently differing opinions on the pleomorphic forms of LCIS and/or LCIS linked to comedo necrosis. These have been proposed to be linked to concurrent invasive carcinoma in as many as 40% of instances [16] and may be categorized as B5 on core needle biopsies [15]. According to the current National Comprehensive Cancer Network guidelines version 2.2017 for breast cancer, excision of pleomorphic LCIS detected on core needle biopsy is also advised [17], while the European Society of Medical Oncology clinical practice guidelines suggest that surgical treatment of pleomorphic LCIS may be comparable to that of DCIS and that radiotherapy may also be considered [16].

The size restrictions of the (p)T1–3 categories do not precisely correspond to the textual specification, however this is not wholly new. The Vernier scales, which use tenth-of-millimeter units, are one method used by certain pathologists to assess tumor size [18]. Taking into consideration the defense to apply this rule for microinvasive carcinomas [2], the practical definitions of tumor sizes change to pT1mi, 0.1–1 mm;

pT1a, 1.1–5.4 mm; pT1b, 5.5–10.4 mm; pT1c, 10.5–20.4 mm; pT2, 20.5–50.4 mm; and pT3, ≥ 50.5 mm while adhering to the rules of rounding to the nearest millimeter.

The diagnosis of the (p)T4d category indicating the presence of inflammatory breast cancer (IBC) may also vary depending on the source. BDiffuse browny induration of the skin with an erysipeloid edge, generally with no underlying mass^, is the remark used to identify this entity in the UICC-TNM books across several editions [1]. The AJCC-TNM8 is considerably more stringent when it comes to classifying a carcinoma as (p)T4d. It is emphasized that IBC is a clinical-pathological diagnosis, meaning that the underlying malignancy must be confirmed pathologically and meet several clinical requirements. At least one-third of the breast must be affected by the diffuse erythema/edema (peau d'orange sign), and the tumor must have progressed quickly—less than six months must pass between the onset of symptoms and the diagnosis of breast cancer [2]. The last suggestion seeks to distinguish IBC from locally progressed breast cancer that later develops inflammatory and cutaneous abnormalities. Dermal lymphatic invasion is common in IBC, although it is not required for diagnosis, nor is its mere presence in the absence of clinical signs of IBC enough to establish this diagnosis and categorization, as the lengthy specification makes apparent [2]. When all of the characteristics of IBC were present but less than one-third of the breast was affected, AJCC-TNM7 addressed the problem by suggesting that these uncommon instances be classified as T4b or T4c [12]. This issue is not specifically covered in AJCC-TNM8, although it seems appropriate to use the prior edition's ruling.

There has been no change to the (p)N categories. It should be emphasized that using pathologic (microscopic) confirming techniques of nodal involvement prior to primary tumor excision leads to a clinical N category for appropriate use. To represent this level of confidence in nodal staging and to compare it with staging based on palpation or imaging (e.g., cN1(f) or cN1(sn) against cN1), qualifiers for either fine needle aspiration cytology or core needle biopsy (f) and sentinel node biopsy (sn) should be placed below. The primary tumor and any lymph nodes must be definitively removed in order to qualify for the pN category [2]. The N0(i+)/cN0(i+) or pN0(i+) categories still represent isolated tumor cells, but the UICC-TNM8 also permits the pN0(mol+) and pN0(mol−) categories to represent isolated tumor cells that were either discovered or tested but not identified by nonmorphological means [1].

Additionally, there have been no modifications made to the M categories. There are no pM0 or Mx categories, despite the existence of the pM1 category (with microscopic proof of distant metastases). As a clinical staging category, isolated tumor cells in distant locations—such as circulating tumor cells in blood or disseminated tumor cells in the bone marrow—are designated M0(i+) or cM0(i+). In order to represent isolated tumor cells found by molecular methods or their absence following molecular testing, the UICC-TNM8 further incorporates the M0(mol+) and M0(mol−) categories [1]. Although a pT and pN category are necessary for the development of pathological stages, the clinical M category or the pathological pM1 category may be used to describe the outcomes of the metastatic work-up.

The biggest size of the largest continuous focus of remaining invasive malignancy, excluding areas of fibrosis inside the tumor bed and the affected lymph node, according to neoadjuvant treatment, determines the ypT and ypN categories. This method may understate remaining tumor burden and deviates from the MD Anderson Cancer Center calculator's estimate of residual cancer burden [19]. In contrast to a post-neoadjuvant therapy micro metastasis consisting of numerous residual nodal tumor foci (none of which exceed 2 mm in greatest dimension) separated by areas of regression-related fibrosis, in a ypN1mi(sn) category, a micro metastasis classified as such prior to neoadjuvant treatment—for example, a cN1mi(sn) category—may indicate a significantly lower tumor burden. Certain nodal metastatic lesions will be classified differently than TNM7 because it was previously unclear why certain areas of treatment-related fibrosis were left out. Even if the metastasis goes away, an original M1 category remains unaffected.

Stages

The definitions of the stages in UICC-TNM7 and UICC-TNM8 are identical; however, there are significant distinctions between UICC-TNM8 and AJCC-TNM8, the latter of which has a dual stage classification. In addition to having the same anatomical stages as UICC-TNM8, AJCC-TNM8 also has more intricate prognostic stages. These are formed from a combination of the T, N, and M categories, and additionally include information on the status of human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER), progesterone receptor (PR), and histological grade. The 21-gene assay was the only one of its kind to achieve level of evidence I at the time of publication [2, 20], hence it is the only one that has been included in the tabulated definitions of prognostic stages. Gene-expression profiles are also included as potential Downstaging criteria for malignancies. Based on a review of the literature and currently unpublished analysis of large datasets [2, 21], the prognostic stages that have been produced represent the prognostic grouping of cancers with similar anticipated survival into a single group (stage) or subgroup (substage). Anatomic stages (UICC-TNM8 stages) and prognostic substages may differ by one or two substages in either direction.

A breast cancer is typically upstaged by PR negative in ER-positive tumors, which is one of the fundamental prognostic staging principles that alters the anatomic stage. The efficacy of targeted antiHER2 treatment has made HER2 positivity a Downstaging factor for the prognostic stages, despite the fact that it was formerly thought to be a factor reflecting a poor prognosis. The prognostic stage of triple-negative cancers is typically upstaged. Depending on additional criteria, histological grade I to III cancers may be upstaged or down staged. Any T1–T2 pN0M0 carcinoma that is ER-positive and HER2-negative and has a recurrence score of less than 11 on Oncotype could optionally be down staged to stage IA, regardless of other factors. Numerous combinations of the seven to eight prognosis stage defining variables have led to a table that is almost four pages long for determining the correct stage. Since this table is difficult to use, electronic versions that aid in determining the prognosis stage may be helpful. One potential method is provided as an appendix to this evaluation in the form of a Microsoft Excel table.

According to the AJCC-TNM8, prognostic stages ought to be applied in regions of the world where the relevant factors are accessible. But in other parts of the world, the factors might be available, but not everyone could receive the targeted treatment [22], which could lead to bias in the staging system. Therefore, having the specified prognostic factor included in the staging system is not enough; the optimal evidence-based treatment must also be provided based on the combination of prognostic and predictive elements. This might potentially be a drawback for testing and retrospective analysis of the new staging method in some regions of the world.

The prognosis variables of breast cancer are not entirely ignored by the UICC-TNM8, which does not mention or fully dismiss the prognostic phases. Instead, it summarizes these factors into the recently proposed prognostic grid, which is neither comprehensive nor free of controversy. The AJCC-TNM8, for instance, lists PR status as a prognostic stage defining factor but does not identify it as an important tumor-related prognostic factor. The AJCC-TNM8 distinguishes between various gene expression profile-based assays based on levels of evidence, and the assay with the highest level has become an optional element in determining prognostic stages. This is also true for tumor profiling, regardless of what this ambiguous phrasing may entail. Although the patient's performance status (and/or the existence of comorbidities) is not stated anywhere, obesity is listed as a patient-related (extra) prognostic factor.

Items that are not included in the most recent editions

The staging manuals did not account for the fact that various nations have implemented breast cancer screening, and that the use of large histological sections and/or magnetic resonance imaging has shown a significantly higher percentage of cases with multiple tumors. In order to differentiate between tumors with a good prognosis and those with a bad prognosis, a large screening trial suggested that 15 mm would be a better cut-off value than 20 mm, even though tumor size is a continuous variable and determining any cut-off value would result in a better prognosis below and a worse prognosis above the cut-off point [23].Even if it did not immediately impact the broader phases, data collection about tumors that fell into the 10.5–15.4 mm range (e.g., pT1c1) and those between 15.5–20.4 mm range (e.g., pT1c2) could have been useful to adhere to the previously introduced and stable pT1a to pT1c subcategories.

The term "multifocality" in breast cancer has at least three different meanings and is somewhat poorly defined. To begin with, a surgical one shows distinct tumors in the same quadrant of the breast. This interpretation is frequently used in relation to the upper outer, lower outer, lower inner, and upper inner quadrants and ignores the fact that an infinite number of quadrants can be created by gradually rotating the four quadrants identified above. Because they are multifocal, some cancers can be brought into the same quadrant by establishing quadrants different than the ones listed above. The second need for a gross interpretation is that each focus be distinct and identifiable either macroscopically or radiologically. Previous TNMs and TNM8 have taken this stance [2]. Thirdly, there is a view that the term "multifocality" should be applied to any tumor focus that is microscopically distinct, and that with this last definition, a worse prognosis is linked to multifocality [24, 25]. Multiple tumor foci can be coded in the T categories by defining

the category by the largest size of the largest invasive tumor focus and then adding a modifier in parenthesis behind it. The modifier could be a number that indicates the number of foci, such as pT1c(m) or pT2(2), or it could be Bm^, which refers to multiplicity. When it comes to phases, the system does not accurately represent the anatomic scope of the disease. The issue is disregarded even in the prognosis stages. Even though the AJCCTNM8 tried to place patients with comparable outcomes in the same prognostic stages while maintaining the same other criteria, multifocal tumors have a higher tumor burden and a worse prognosis than their unifocal but identically registered and staged counterparts. This is an illustration of how the problem of prognostic group formation may not have been resolved by prognostic phases. Although multifocality affects results [26], the UICCTNM8 prognostic grid makes no mention of it. The prognostic grid [1] and the prognostic stages [2, 32] do not use or mention other parameters that may have an effect on prognosis or treatment prediction, but lack sufficient evidence (e.g., diffuse distribution of the in situ and/or invasive components and extent of disease [27, 28]), reproducibility (e.g., Ki67, tumor-infiltrating lymphocytes [29, 30]), and/or relatively uniform availability (e.g., urokinase plasminogen activator and plasminogen activator inhibitor type 1 (uPA, PAI-1) [31]).

Several institutes use molecular testing of sentinel lymph nodes as an intraoperative evaluation method. A greater portion of the lymph node is frequently used for the molecular assay, despite current guidelines recommending that at least some of the tissue be examined by microscopy. Quantitative molecular assays, including one-step nucleic acid amplification, have been shown to be accurate [33, 34] and can detect involvement of tumor cell types other than isolated ones. Although it has not been included in TNM8, there have been proposals to call this pN1(mol+) [33, 35]. It is surprising that the prognostic factors have not affected stage IV. The illness is placed in the worse prognostic and anatomic stage whenever M1 (distant metastasis) is present, and stage IV is the same for both. There are, nevertheless, long-term survival of stage IV breast cancers [36], and these individuals must differ from those who pass away within a few months in terms of disease-host-treatment interactions and characteristics. As evidence, we showed that patients with triple-negative tumors had a lower survival rate than those with ER-positive HER2-negative tumors in stage IV breast cancer, based on ER, PR, and HER2 statuses [37].

Concluding observations

In subsequent years, the usefulness of prognostic stages will be elucidated. In order to enable a more individualized classification of patients, this is a valuable attempt to categorize patients based on their prognosis beyond the anatomic extent of their disease [4]. Adding a prognosis scoring system to TNM without changing its fundamental structure is undoubtedly not the only way to achieve this goal (as with the prognostic stages in AJCCTNM8). Examples include computer-based multivariate predictive models such as the temporarily non-functioning Adjuvant!Online [38] or PredictPlus [39], or modifiers (ER, PR, HER2 statuses, grade, proliferation index, gene expression-based scores, etc.) taken into consideration in addition to the anatomic stage (as typically used in treatment decision-making and as expected on the basis of UICC-TNM8).With new treatments, companion tests or predictive markers, and new evidence to keep patients with

similar outcomes in the same group (prognostic substage), the system of prognostic stages will need to be continuously maintained. Because of this, it is probably going to undergo greater and faster changes than the physical stages, and rapid linguistic alterations could change comprehensibility. According to the authors of the breast chapter in AJCC-TNM8 [1], the implementation of prognostic stages divides the world between regions where anatomic staging will be the sole staging option available and regions where prognostic stages can be used. The oncological community and cancer registries also have a say in whether they employ the UICC-TNM8 and its stages, which are considered international due to their name, or the more thorough and useful AJCC-TNM8 and its prognostic stages, which are American in name. The stages should therefore also be classified as prognostic or anatomic in the exchange of results between various centers, having in mind that the prefix Ba^ may imply autopsy-based staging and the prefix Bp^ is already used to reflect pathological stages rather than clinical stages. Whether the differences between UICC-TNM8 and AJCC-TNM8 and the staging methods based on them are beneficial or harmful would be difficult to determine, but it is clear that the common language of cancer staging has weakened, and more details will be needed to prevent misunderstandings.

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