

**COMMUNICATION**

*from the International  
Union Against Cancer and  
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## On the Use and Abuse of X in the TNM Classification

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**T**he tumor, lymph node, metastasis (TNM) classification system that has been in use worldwide since the 1980s<sup>1</sup> was built on the premise that the anatomic extent of a majority of solid tumors is one of the most robust prognostic markers in cancer management. The TNM system is used by physicians and cancer registrars to categorize patients into important groups for treatment planning, clinical trials, and follow-up management.

Although the TNM system has been evolving since the late 1940s,<sup>2</sup> important additions to the staging taxonomy have mandated the development of important revisionary milestones, which add new clinical, pathologic, and molecular markers to the foundation of the system represented by the tumor, lymph node, and metastatic categories. The latest, sixth edition of the International Union Against Cancer (UICC)<sup>3</sup> and American Joint Committee on Cancer (AJCC)<sup>4</sup> continues this tradition and attempts to define parameters to reduce the subjectivity of cancer staging.

Through discussions with physicians and registrars and through review of inquiries to the UICC and AJCC seeking clarification of staging guidelines, there remain areas of elusiveness and uncertainty in assigning proper staging categories. One of the most frequent of these conundrums is in the use of the "X" suffix, especially when assigned to the N or M categories. The proper use of X is to denote the absence or uncertainty of assigning a given category (T, N, or M) when all reasonable clinical or pathologic maneuvers have been used in staging.<sup>5</sup> To aid the clinician in the approach to lymph node staging, the pertinent literature<sup>3,4</sup> has offered guidelines indicating the optimal number of lymph nodes that should be assessed pathologically to adequately stage a given solid tumor. It has become clear that improvements in staging and prognosis may depend heavily on the removal of a maximum number of lymph nodes whether these are positive or negative for tumor cells.<sup>6,7</sup>

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The significance of this problem is that when TX, NX, or MX is used, patients cannot ordinarily be assigned a stage, e.g., Stage III. Therefore, data may not be recorded in cancer registries or may be rejected from studies.<sup>8</sup> The objective of this communication is to clarify the use of X.

The ongoing confusion regarding the use of the lymph node guidelines is manifest by the increased association of the X suffix along with the N category when the optimal number of lymph nodes has not been assessed. Clinicians have been reticent to assign the pN0 designation, because the lymph node count has not reached a prescribed benchmark. Both the UICC and AJCC staging references,<sup>3,4</sup> as well as subsequent editorials,<sup>9</sup> have stressed that the pN0 designation, which indicates an absence of malignant cells in the extirpated lymph node basin, can be rendered appropriately even though fewer than the optimal numbers of lymph nodes have been assessed. In these circumstances, the pN0 designation should be entered on the staging forms and placed into cancer registry documents. Accurate reporting of the number of lymph nodes removed and pathologically analyzed is mandatory and should be used as a quality indicator for both the surgeon and the pathologist. Appropriate assignment of the stage group, however, depends on the appropriate use of pN0 and not pNX. The designation pNX is appropriate only if no lymph nodes are resected or examined.

Similarly, a trend has developed in which physicians have become hesitant to assign the M0 category when there are no obvious indicators of systemic metastatic spread of cancer. Some have taken the approach that, despite the use of all reasonable staging modalities (bone scans, computed tomography scans, magnetic resonance images, positron emission tomography scans, etc.), the remote possibility of cellular spread warrants the MX designation. A small but vocal group (unpublished observations) has taken the position that assigning an M0 designation presents a medicolegal problem for the staging physician, because metastases could appear at any time in the future!

Both the AJCC and the UICC have stated clearly that appropriate staging should be based on reasonable judgment and the application of appropriate imaging studies according to organizational guidelines, clinical pathways, or the medical standards in place in a given location.<sup>10</sup> In situations in which doubt exists or equivocal information is obtained, the assignment of a lower stage or category should ensue and, indeed, is a rule of TNM.<sup>3-5</sup> In essence, Rule 4 of the general rules of the TNM system states that, if there is doubt concerning the correct category to which a particular

patient should be allotted (T, N, or M), then the lower (i.e., less advanced) category should be used. The M1 designation should not be used except when clear indications of clinical or pathologic distant metastases are evident. The MX designation is assigned properly when studies have not been performed to adequately assess the presence of metastases. However, according to the *Rules for Classification* section in the TNM classification, at the majority of tumor sites, the procedures for assessing the M category are "physical examination and imaging."<sup>3</sup> Some sites (e.g., the digestive system, lung, and pleura) specify "physical examination, imaging, and/or surgical exploration." At a few sites, biochemical tests are required to adequately assess the M category in addition to physical examination and imaging studies (e.g., prostate and testis). Except for the prostate, where skeletal studies are mentioned, the actual imaging studies are not specified, because their availability varies worldwide. Therefore, for most sites, if physical examination and a chest radiograph show no obvious metastasis, then an M0 designation is warranted. Likewise, if, during a colectomy for carcinoma, the liver and peritoneum obviously do not contain tumor, then an M0 designation is justified. The MX designation, therefore, is the exception rather than the rule and is justified only if there is no examination or investigation for metastases. From a medicolegal standpoint, the general procedures described in the *TNM Rules for Classification* should be the guideline.

Although it is less frequent than uncertainty in the appropriate use of NX and MX, confusion sometime also arises in the use of TX. Although it may be used in the context of an unknown primary tumor, this is incorrect. TX means that the tumor was not able to be evaluated, whereas T0 means that there is no evidence for a primary tumor. Therefore, when a cervical lymph node biopsy reveals squamous cell carcinoma compatible with a head and neck primary tumor, but examination and investigations fail to reveal a primary tumor, T0 is the appropriate designation. TX is appropriate only if the presumed primary tumor cannot be evaluated.

It is essential to avoid the abuse of X. It should not be used to simply fill in the blanks when someone has neglected to apply an N or M designation when a patient was seen, despite the presence of relevant information at the time and before treatment. Such an approach is unhelpful and, indeed, is not permitted by the TNM convention. X has particular meaning, as discussed above, and blank spaces should be left blank—evidence that the registry or the physician has not performed their task (an important part of the audit trail). It is important that we use the X factor in

the correct manner, because the opportunity for auditing stage data, stage grouping our patients, and recording them in cancer registries is hampered when X is applied indiscriminately. Appropriate staging of cancer patients should be our overriding goal. The tenets of TNM provide the framework. It is our challenge to use the framework correctly.

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