Classification of Isolated Tumor Cells

Clarification of the 6th Edition of the American Joint Committee on Cancer Staging Manual

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In May 2002, the 6th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual was published, and the new staging system was officially adopted for use in tumor registries in January 2003. The changes adopted for the chapter concerning breast carcinoma were the result of recommendations made by a task force comprising internationally recognized experts in the field of breast carcinoma management. This task force was charged with proposing changes that reflected published clinical data and current clinical consensus.

Although the breast carcinoma staging system presented in the 6th edition includes much-needed changes reflecting contemporary standards of care, it is undeniably more complex than the system presented in previous editions of the staging manual. This is especially true of the new material dealing with the distinction between isolated tumor cells and micrometastases. With the increasing use of sentinel lymph node biopsy, immunohistochemical (IHC) staining, and molecular biologic techniques, pathologists can more easily detect microscopic lesions at the level of isolated tumor cells. We do not yet know whether these isolated cells have any clinical significance, and the accrual of relevant data has been hindered by the lack of a clear quantitative distinction between isolated tumor cells and micrometastases. The 6th edition of the AJCC Cancer Staging Manual has made this distinction based on size; isolated tumor cells are defined as metastatic lesions no larger than 0.2 mm in dimension and classified as pN0, whereas micrometastases are defined as metastatic lesions larger than 0.2 mm in dimension but no larger than 2.0 mm in dimension and classified as pN1mi.

The AJCC Cancer Staging Manual is an evolving document. Even as one revision is published, new information is coming to light that will ultimately mandate the need for future editions. Since the publication of the 6th edition, task force members have fielded a large
number of questions concerning the new system. Although the majority of these questions have dealt with problems of interpretation, a few have suggested potential clinical situations that do not appear to be covered by the staging guidelines. One such situation has to do with the correct use of identifiers for isolated tumor cells.

In the 6th edition of the *AJCC Cancer Staging Manual*, it was recognized that virtually all isolated tumor cells are detected using IHC staining techniques. To reflect this, the staging designation pN0 was given an additional identifier (i) for “immunohistochemical” in cases that are histologically negative based on hematoxylin and eosin (H & E) staining for lymph node metastases and in which IHC techniques are used. For example, the designation pN0(i+) would indicate a case that was H & E-negative on initial examination, but in which an isolated tumor cell deposit no greater than 0.2 mm in dimension was identified by IHC. In this way, outcome data related to the presence of these minute lesions could be accrued in a uniform manner.

Although this approach is broadly applicable in the majority of cases, it does not cover all cases. It is technically possible, although predictably rare in practice, to detect isolated tumor cells (single cells or small cell deposits) in otherwise lymph node-negative patients using H & E staining. As originally written, the new AJCC staging system for breast carcinoma would not record these small lesions. The TNM staging system published by the International Union Against Cancer (UICC) to coincide with the new edition from the AJCC differs slightly in this specific definition. They use the identifier (i) to indicate “isolated tumor cells” rather than “immunohistochemical.” Thus, any lesion measuring ≤ 0.2 mm in greatest dimension, regardless of the staining technique used to identify it, would be designated as pN0(i+).

To be consistent with the updated UICC classification, the following clarification is made to the AJCC classification: the identifier (i) will be used to indicate “isolated tumor cells.” All metastatic lesions no larger than 0.2 mm, whether detected by H & E or IHC, will be designated as pN0(i+), while a designation of pN0(i-) will be used to indicate no detectable tumor cells by either H & E or IHC. The designation pN1mi with no additional identifiers will be used for micrometastases greater than 0.2 mm but no greater than 2.0 mm in greatest dimension.

**REFERENCES**