Changes and Problematic Areas in Interpretation of the AJCC Cancer Staging Manual, 6th Edition, for Breast Cancer

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• Context.—Tumor stage is an important prognostic factor and guides therapy for patients with breast cancer. The American Joint Committee on Cancer (AJCC) periodically updates the staging standards. This article describes changes and problematic areas in interpretation of the AJCC Cancer Staging Manual, 6th edition, for breast cancer and provides practical advice.

Objectives.—This article reviews the variety of practical problems that can arise during assessment of the pathologic stage and other prognostic/predictive factors included in the College of American Pathologists Checklist for Evaluation of Resected Breast Cancers. Potential practical difficulties that can arise include the classification of lymph nodes, for example, isolated tumor cells, micrometastases, metastases, and the combination of locations. Another difficult area is assignment of a correct size. The use of clinical and imaging studies for optimal pathologic staging is discussed. Finally, the proper use of the TNM descriptors is described.

Conclusions.—The various practical problems that can arise during the assessment of important prognostic and predictive features included in the College of American Pathologists Checklist for Evaluation of Resected Breast Cancers are discussed, and specific recommendations are given.

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Since publication in 2002, there have been changes or clarifications primarily in what is considered the classification of pN0(i) and in the definition of isolated tumor cells (ITCs).1 In the AJCC Cancer Staging Manual, 6th edition, published in 2002, pN0(i−) was classified as no regional lymph node metastasis histologically, negative immunohistochemistry (IHC). The pN0(i+) classification as of publication in 2002 was no regional lymph node metastasis histologically, positive IHC, and no IHC cluster greater than 0.2 mm. The classification of pN1mi(i+) as of publication in 2002 was micrometastasis detected only by IHC.2

In late 2003, changes or clarifications to these classifications were made for regional lymph nodes (pN), and the definitions of pN0(i+) and pN0(i−) were updated to indicate that i− refers to the presence or absence of ITCs detected by any morphologic technique, including hematoxylin-eosin staining and IHC.1 The reporting element pN1mi(i+) was eliminated, and pN0(i−) became regional lymph node metastasis histologically, negative morphologic findings for ITCs (any morphologic technique, including hematoxylin-eosin and IHC).

pN0(i+) now reads no regional lymph node metastasis histologically, positive morphologic findings for ITCs (any morphologic technique, including hematoxylin-eosin and IHC), and no ITC cluster greater than 0.2 mm.3

CLASSIFICATION OF ISOLATED TUMOR CELLS

The classification of ITCs seems straightforward, that is, ITCs with no cluster larger than 0.2 mm (Figure 1). Other than this statement, no guidelines have been elaborated. The following examples are unofficial and represent how I personally would interpret different situations.

A not uncommon occurrence is finding more than 1 group of cells that individually would qualify as ITCs (Figure 2). This example could be classified as a lymph node with 2 groups of ITCs, pN0(i+), or if one includes the distance between the 2 groups in the measurement, it would be classified as pN1a. I believe the intent would be to classify this as a lymph node with 2 groups of ITCs, pN0(i+) rather than pN1a.

Another common occurrence is diffuse involvement by ITCs, as is often seen with infiltrating lobular carcinoma (Figure 3). While these are truly ITCs, I believe the intent would be to classify this as node positive (pN1a), based on the number of tumor cells.

PATHOLOGIC STAGING

It is important for pathologists to be aware of the elements of clinical staging because some of these can be used by pathologists to fill voids in pathologic staging. Pathologic staging includes all data used for clinical staging plus data from surgical exploration and resection.2

“Imaging findings within 4 months of diagnosis in the absence of disease progression or through completion of surgery(ies), whichever is longer” are considered elements of staging.2 Such imaging findings would include the size of staging.
Figure 1. Diagrammatic representation of isolated tumor cells (ITCs). Isolated tumor cells are defined as no regional lymph node metastasis histologically, positive morphologic findings for ITCs (any morphologic technique, including hematoxylin-eosin and immunohistochemistry), and no ITC cluster greater than 0.2 mm. The node shown would be classified as pN0(i+) because there is a single focus of tumor that measures 0.1 mm.

Figure 2. Diagrammatic representation of a lymph node with 2 groups of tumor cells, each measuring 0.1 mm. There are no written guidelines for classification. I would recommend classifying this example as a lymph node with 2 groups of isolated tumor cells. Others would measure the greatest distance and classify this as pN1a.

Figure 3. Diagrammatic representation of a lymph node with numerous isolated tumor cells. This pattern is commonly seen with infiltrating lobular carcinoma. I would classify this example as a positive node (pN1a).

Figure 4. Tumor size. This diagram shows one reason that adding the size of tumors from 2 specimens is not appropriate for staging.

Figure 5. Tumor size. How far apart do tumor nodules have to be to be considered separate? Again, there are no written guidelines. I would recommend that if they are clearly separate, the largest be measured for pT size. If they are close, I would refer to imaging studies if possible.

Figure 6. Tumor size. How far apart do tumor nodules have to be to be considered separate? If imaging or other examinations indicate 1 lesion, measure the greatest dimension. If imaging or other examinations indicate multiple lesions, measure the largest.
of the primary tumor, chest wall invasion, and the presence of regional or distant metastases. The pathologic tumor size (pT) can be assigned with microscopic, but not macroscopic, tumor at margins. With macroscopic tumor at margins the classification is pTX.

If a tumor is grossly cut across and there is significant tumor in a subsequent excision, an accurate pT classification cannot be assigned. It is very important to know that it is not permissible to add sizes together. I like to use the example of an orange cut in half. An 8-cm orange cut in half gives two 8-cm-diameter halves. The entire orange is 8 cm and not 16 cm (Figure 4). With 2 specimens, one could use the largest measurement and report the tumor as “at least pT2.” A more accurate estimate may be based on imaging studies.

Pathologic stage groupings may include any combination of pathologic and clinical classifications. For example, pT N cM.

\[ \text{pT} \quad \text{pN} \quad \text{cM} \]

The measurement used for classifying the primary tumor (T) is the one judged to be most accurate for that particular case (ie, physical examination or imaging, such as mammography or ultrasound).²

**PATHOLOGIC TUMOR SIZE (pT)**

The pathologic tumor size (pT) for the T classification is a measurement of the invasive component only. For example, if there is a 4.0-cm intraductal component and a 0.3-cm invasive component, the tumor is classified pT1a. This is an extremely important point. The size of the invasive tumor should be verified microscopically. This recommendation does not imply that the size measured on the slide replaces the gross measurement. The microscopic examination verifies that what is seen grossly is in fact invasive carcinoma. If the microscopic examination reveals that the gross “mass” is mostly ductal carcinoma in situ (DCIS) or a biopsy site reaction, measurement on the slide(s) may be a more accurate at establishing the true invasive size.

In patients who have undergone multiple core biopsies, measuring only the residual lesion or the largest size on the core biopsy may result in significant understaging of the primary tumor. If the microscopic examination reveals that the largest focus is used to classify the microinvasion.² When there are multiple foci of microinvasive carcinoma, it is not appropriate to add them together. The presence of multiple foci of microinvasion should be noted and/or quantified, as it is with multiple larger invasive carcinomas.

**MICROINVASION OF BREAST CARCINOMA**

Microinvasion is the extension of cancer cells beyond the basement membrane into the adjacent tissues with no focus more than 0.1 cm in greatest dimension. When there are multiple foci of microinvasion, the size of only the largest focus is used to classify the microinvasion.² When there are multiple foci of microinvasive carcinoma, it is not appropriate to add them together. The presence of multiple foci of microinvasion should be noted and/or quantified, as it is with multiple larger invasive carcinomas.

**MULTIPLE SIMULTANEOUS IPSILATERAL PRIMARY CARCINOMAS**

Multiple simultaneous ipsilateral primary carcinomas are defined as infiltrating, macroscopically measurable carcinomas. Use the largest primary carcinoma to designate T classification. It is not appropriate to assign a separate T classification for the smaller tumor(s); however, one should record that this is a case of multiple simultaneous ipsilateral primary carcinomas.²

A major unanswered question is how far apart tumors have to be to be considered separate (Figure 5). If the foci are clearly separate, measure the largest for pT. This area requires a lot of judgment. When they microscopically appear very close, my recommendation would be if imaging or other modalities indicate 1 lesion, measure the greatest dimension. If on the other hand imaging or other modalities indicate multiple lesions, measure the largest (Figure 6).

**SKIN OF BREAST**

**Inflammatory Carcinoma**

Inflammatory carcinoma is a clinicopathologic entity characterized by diffuse erythema and edema (peau d’orange) of the breast, often without an underlying palpable mass. These clinical findings should involve the majority of the skin of the breast.² It is important to remember that inflammatory carcinoma is primarily a clinical diagnosis. Involvement of the dermal lymphatics alone does not indicate inflammatory carcinoma in the absence of clinical findings.

\[ \text{pT4} \]

pT4 is a tumor of any size with direct extension to chest wall or skin, only as described as follows.

- T4a is defined as extension to chest wall, not including pectoralis muscle.
- T4b is defined as edema (including peau d’orange) or ulceration of the skin of the breast, or satellite skin nodules (grossly, not only microscopically seen) confined to the same breast. Since diffuse peau d’orange would be inflammatory carcinoma (T4d), I would assume that T4b would include limited skin edema.

Importantly, other skin changes, such as dimpling of the skin, nipple retraction, or any other skin change (except those described under T4b and T4d) may occur in T1, T2, or T3 without changing the classification.²

**REGIONAL LYMPH NODES (N)**

The new nodal classification has many categories that are easy to understand, but some may either cause co-
fusion or be difficult for the pathologist to apply. The major classification change is that the number of involved nodes dramatically changes the N stage.

The overall classification is based on axillary lymph node dissection, with or without sentinel lymph node dissection. If the classification is based solely on sentinel lymph node dissection without subsequent axillary lymph node dissection, it is designated (sn) for sentinel node, for example, pN0(sn). Intramammary lymph nodes are classified as axillary lymph nodes. Cancerous nodules in the axillary fat without evidence of residual lymph node tissue are classified as positive axillary lymph nodes (N).

pN1 is the classification for micrometastases, which is a metastasis greater than 0.2 mm with none greater than 2.0 mm. Therefore, if there is 1 metastasis greater than 2 mm and 3 micrometastases, it would be counted as 4 positive nodes. On the other hand, if there is 1 metastasis greater than 2 mm and 3 nodes with ITCs, I would recommend counting this case as 1 positive node.

pN1 is the category for metastasis in 1 to 3 axillary lymph nodes and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection, but not clinically apparent. This raises the question as to what clinically apparent stands for. Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically. Conversely, not clinically apparent is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.

pN1a is metastasis in 1 to 3 axillary lymph nodes. pN1b is metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection, but not clinically apparent. Again, this classification will be rarely used. If associated with greater than 3 positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden.

pN2a now stands for metastasis in 4 to 9 axillary lymph nodes (at least 1 tumor deposit greater than 2.0 mm). pN2b is metastasis in clinically apparent (histologically confirmed) internal mammary lymph nodes in the absence of axillary lymph node metastasis.

pN3a now stands for metastasis in 10 or more axillary lymph nodes (at least 1 tumor deposit greater than 2.0 mm) or metastasis to the infracavicular lymph nodes. pN3b is metastasis in clinically apparent ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes, or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection, but not clinically apparent. pN3c is metastasis in ipsilateral supraclavicular lymph nodes. Metastasis to any other lymph node, including cervical or contralateral internal mammary lymph nodes, is classified as distant (M1).

HISTOLOGIC GRADE

All invasive breast carcinomas, with the exception of medullary carcinoma, should be graded. This includes invasive lobular and mucinous carcinomas. The Nottingham combined histologic grade (Elston-Ellis modification of the Scarff-Bloom-Richardson grading system) is recommended.

TNM DESCRIPTORS

The TNM descriptors are for identification of special cases of TNM or pTNM classifications; the “m” suffix and “y,” “r,” and “a” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses, for example, p(m)T(N). The “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor prior to multimodality therapy (ie, before initiation of neoadjuvant therapy).

The ypTNM may be misleading. The most important predictor of prognosis depends on the response of the tumor to treatment. Patients with advanced disease with a complete pathologic response have an excellent prognosis. Patients with advanced disease with only a partial response have a very poor prognosis, even when they obtain a favorable ypTN classification.

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval and is identified by the “r” prefix, for example, rTNM.

The “a” prefix designates the stage determined at autopsy, for example, aTNM.

RESIDUAL TUMOR (R)

Tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, as follows.

RX Presence of residual tumor cannot be assessed,
R0 No residual tumor,
R1 Microscopic residual tumor,
R2 Macroscopic residual tumor.

During the past few years there have been a number of questions concerning implementation of the College of American Pathologists cancer protocols. The protocols reflect the AJCC 6th edition. The following are questions not already addressed in this article.

Q. In the Nottingham histologic scoring for invasive breast tumor, is it mandatory to report the actual mitotic count and total Nottingham score?
A. If you report histologic grade by the combined Nottingham score, scores for each of the 3 elements (score 1, 2, or 3) will be required (as well as the total score), but you will not have to separately list a specific mitotic count in addition to the score.

Q. If the Nottingham histologic scoring system for invasive breast tumor is not used, is it mandatory to report the actual mitotic count and total Nottingham score?
A. In contrast, a specific mitotic figure count will be re-
quired for those who report histologic grade by a system other than Nottingham.

Q. Are checklists necessary for core biopsies?
A. No. Checklists are for excision specimens.

Q. Do you report out items from the first specimen on the second? Do you note it some special way?
A. The gross and microscopic diagnoses of an individual pathology report are primarily concerned with that specimen, but the tumor summary (our wording) or checklist can and should include information obtained from earlier specimens. For instance, estrogen receptor, progesterone receptor, and HER-2 evaluations may have already been done on the needle biopsy, or perhaps a sentinel lymph node biopsy was done on an earlier excision.

Q. Do reports for DCIS only need use the breast checklist?
A. No.

Q. Are College of American Pathologists protocols required for both lumpectomy and a subsequent mastectomy?
A. It depends on the findings in the mastectomy speci-

men. If there are no changes in the required elements, no protocol would be necessary. If there are changes in the required elements, those elements at least would have to be reported.

I hope these observations have helped clarify issues with the current staging system.

References