

# At Last—Worldwide Agreement on the Staging of Cancer

## Presidential Address

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The current TNM system for classification and staging of cancer approved by both the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre le Cancer/TNM Committee (UICC/TNMC) is designed primarily for patient care and, in this context, is equally applicable to patients in clinical research, community hospitals, and developing countries. Flexibility in its use has been accomplished with a telescoping format where applicable, permitting the use of only major headings with fewer cases and ramification of the major headings to smaller subsets with larger numbers of cases, allowing for comparison of both types of data from anywhere in the world.

### TNM HISTORICAL NOTES

Many of you in the audience have participated in the development of this system and can appreciate the value of worldwide agreement in staging as well as the problems inherent in reaching agreement. It has been a long process involving a legion of two generations of oncologists over four decades, with the final efforts for worldwide agreement taking place from 1982 through 1986. Rubin<sup>1</sup> reviewed the history of staging, which started in the 1920s with the League of Nations. Harmer<sup>2</sup> appropriately credited the origin of the TNM concept for the classification of cancer to Denoix during the years 1948 through 1952. Gerald P. Murphy, MD, secretary-general of the UICC, recently wrote to Pierre Denoix, MD, informing him of UICC plans to celebrate 50 years of the TNM classification in 1995 (personal communication, March 15, 1987). In 1954, the UICC initiated activities in the clinical staging of cancer

based on the anatomic extent of disease derived from the TNM classification: T, extent of primary tumor; N, absence or presence and extent of regional lymph node metastasis; and M, absence or presence of distant metastasis. Later, in 1959, the AJCC (formerly the American Joint Committee on Cancer Staging and End Results Reporting) was formally established. The following organizations sponsor the AJCC: American Cancer Society, American College of Physicians, American College of Radiology, American College of Surgeons, College of American Pathologists, and National Cancer Institute. In addition, liaison members include the American Urological Association, Association of American Cancer Institutes, American Academy of Pediatrics, and National Tumor Registrars Association. Funding of the AJCC has been provided by grants from the American Cancer Society and the National Cancer Institute; the AJCC is administered by the American College of Surgeons, Oliver H. Beahrs, MD, executive director.

The following national committees and international organizations sponsor the UICC/TNMC: AJCC, British Isles Joint TNM Classification Committee, Canadian National TNM Committee, Deutschsprachiger TNM-Ausschuss (Kommission), European Organization for Research on Treatment of Cancer, Fédération Internationale de Gynécologie et d'Obstétrique, International Commission on Stage Grouping in Cancer and the Presentation of Results of the International Society of Radiology, Japanese Joint Committee, and La Société Internationale d'Oncologie Pédiatrique.

It is evident from the above that the representation on, interest in, and support of the AJCC and UICC/TNMC are now broad based and quite universal. However, in the past, various groups independently adopted their own unique variations for the classification of certain types of tumors. To introduce standardization so that data throughout the world could be compared, the national TNM committees agreed in 1982 to formulate a universal TNM classification and stage grouping. Harvey W. Baker, MD, my predecessor as chairman of the AJCC, recently wrote to me (personal communication, March 2, 1987) and enclosed a copy of a letter dated Oct 14, 1981, from Mr Michael Harmer<sup>3</sup> (editor

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of the first three editions of the *UICC Classification of Malignant Tumors*) to the editor of the *International Journal of Radiation Oncology, Biology, Physics*. It was this letter that prompted Dr Baker to initiate the liaison activities that culminated in the agreement we now have. These are some of Mr Harmer's general comments:

everyone agrees in general: no one agrees in particular . . . The Devil lurks in the details . . . any international classification is better than half a dozen national classifications. (But *per contra*, as Dr. Haagensen remarked when debating the relative merits of the Columbia breast staging and the UICC Classification with me on one occasion: 'because a thing is international it does not follow that it is necessarily best.')

In 1968, after attending a meeting of the AJCC on behalf of the UICC, Mr Harmer wrote a memorandum that he excerpted in his letter and bears repeating; it was titled "Failure of a Mission:"

At the end of a somewhat abrasive debate in which Mr. Harmer reproached the AJC for lack of cooperation, Dr. Murray Copeland, summing-up from the Chair and anxious to pour oil upon troubled waters, observed that at least the AJC and the UICC 'would continue to cooperate along parallel lines.' To which Mr. Harmer replied that, by definition, parallel lines met at infinity.

Mr Harmer also noted that the third edition of the UICC *Livre de poche* had 28 site classifications but only one was identical in content with the classifications in the *AJCC Manual for Staging of Cancer*; this was for the breast. He commented that "herein lies the opportunity for consensus—or chaos!"

Finally, Mr Harmer's conclusion was prophetic:

It is this 'solution' which I am now bold enough to suggest. That an International Commission should be assembled (under whose auspices to be determined) and at which the TNM system of classification for all anatomical sites of malignant tumors should be agreed for publication in 1986. Then, and only then, will we be able to equate with Saint Thomas Aquinas and claim with him: 'They are wise who put things in their right order.'

Well, history tells the rest of the story. Drs Baker and Beahrs accepted the challenge and convened an exploratory meeting during the International Cancer Congress in Seattle in 1982. This positive exploratory effort was then reinforced with several subsequent working liaison meetings facilitated by Leslie H. Sobin, MD, the current chairman of the UICC/TNMC. Mr Harmer's exhortation catalyzed the essential activity, and as he wished, international agreement was achieved in 1986 with the approval of all national TNM committees. The AJCC and UICC publications of the current system for classification and stage grouping of cancer will appear in 1988 and 1987, respectively. It is the intention of the national committees that the classifications in these publications remain unchanged until some major scientific advance mandates reconsideration.

### PRINCIPLE OF TNM

The principle of the TNM system is to classify tumors by their anatomic extent using the TNM categories and then to group combinations of the TNM into prognostically similar categories called stages. The general principle of staging at all sites is to number from best (stage 0) to poorest (stage IV) survival: stage 0, carcinoma in situ; stage I, localized cancer; stage II, limited local or regional spread; stage III, extensive local or regional spread; and stage IV, distant spread.

### PURPOSE OF TNM

The purpose of TNM classification and staging is to categorize patients into stage groups of similar anatomic

extent of cancer for the following reasons: (1) to select appropriate standard treatments, (2) to evaluate the results of new treatments, (3) to acquire data in an orderly fashion for statistical analysis of end results, and (4) to estimate prognosis. Furthermore, since all of the national TNM committees have agreed on the definitions for classification, data throughout the world can be compared.

### GENERAL AGREEMENTS IN TNM CLASSIFICATION

I will explain what has happened during the years of ecumenism, 1982 through 1986, first in general terms about staging at all sites and then with one typical example—the classification and stage grouping for breast cancer.

The general agreements applicable to all anatomic sites include the same format and wording, in so far as possible, for definitions of classifications at all anatomic sites: Tx, primary tumor cannot be assessed, and T<sub>—</sub>, a tumor more than — cm but not more than — cm in greatest dimension. In our effort to be precise, we avoided subjectivity as much as possible by eliminating such terms as operable, inoperable, curative, movable, fixed, and matted. We preferred to use objective criteria such as size and number (eg, of lymph nodes with metastases) whenever possible. Stage 0 is used for carcinoma in situ (Tis N0 M0), and the previous (AJCC) classification of "juxtaregional lymph nodes" has been eliminated. Juxtaregional lymph nodes at all anatomic sites were reclassified as either regional (N) or distant (M). The "Surgical Evaluative Stage" used by the AJCC was eliminated. Now there are two major stage groups. The clinical stage (cTNM classification) is an expression of the anatomic extent of disease based on pretreatment clinical evaluation and microscopic examination of tissues (of lesser extent than required for pathologic classification). The pathological stage (pTNM classification) includes the pretreatment clinical data plus additional evidence gleaned after surgical resection and pathological examination of tissues adequate to evaluate the highest pT and pN categories. Pathological classification of distant metastasis (pM) entails microscopic examination.

In the major effort to add precision and eliminate ambiguity in the definitions of the classifications, each anatomic site task force reviewed the classifications for its site. When the task force concurred, the classifications and stage groups were next reviewed by the appropriate national committee, then by the AJCC and the UICC/TNMC independently, and finally by the AJCC-UICC/TNMC Liaison Committee. This last committee, at its several meetings, scrutinized and often debated every word of every line of every definition at every anatomic site. Finally, there were several joint meetings of the editorial committees of the AJCC and UICC/TNMC to be certain that the definitions in each publication are the same. The third edition of the AJCC's *Manual for Staging of Cancer* (published by JB Lippincott, Philadelphia) will have the same large format as the second edition, and the fourth edition of the UICC's *TNM Classification of Malignant Tumors* (published by Springer-Verlag NY Inc, New York) will be available in its familiar pocket-sized (*Livre de poche*) edition.

In addition to clarifying the definitions, some definitions were significantly revised. The regional lymph nodes of the neck are classified the same way for all head and neck sites (except thyroid)—by size and number of metastases. The thyroid cancer classification was redone and improved. Significant clarifications and improvements were made in the classification of lung cancer and melanoma of skin. The classification of genitourinary tumors was completely revised and greatly simplified. The classification of tumors of the liver, gallbladder, and biliary tree was significantly

revised and improved. Primary tumors (T) of the esophagus, stomach, and colorectum are all classified by the depth of invasion into the wall. Tumors of the anal canal (T) are classified by the greatest dimension (since currently they are infrequently totally resected).

The stage grouping for carcinoma of the colorectum has been revised and is now compatible with the previous German, Japanese, and Dukes systems: Dukes A, stage I; Dukes B, stage II; and Dukes C, stage III.<sup>4</sup> Furthermore, within each stage grouping there are TNM subsets adding greater specificity, and, additionally, there are stage 0 (carcinoma in situ) and stage IV (distant metastasis).

The AJCC, UICC/TNMC, and Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) each believed that the FIGO classification for gynecologic tumors was identical as used by all. However, it became evident when a liaison committee of all three groups sat together to compare manuscripts that there were significant differences. There was adjudication of many of the differences (capitulation on some), and one system has been redrafted in the format of TNM to be used by the AJCC, FIGO, and UICC.

Similarly, the AJCC and UICC/TNMC each believed it was using the 1971 Ann Arbor classification for Hodgkin's disease until they sat together for a line-by-line review. These differences have been resolved, ambiguities have been removed from the classifications, and now both editions are identical. Finally, the AJCC manual will have a section at the end of each chapter noting any changes from the previous edition.

Statistical data from various reference sources have been used in the development of these systems, such as the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, the Erlangen Registry (Germany), and the Japanese Joint Committee, to cite but a few.

Now let me be more specific and use one anatomic site as an example—the breast. Revisions were made in the 1982 UICC and 1983 AJCC editions to accommodate the then-new information on minimal breast carcinoma (pT) and micrometastasis (pN). In anticipation of the new editions, the Breast Task Force met to review, clarify, simplify, and modify as indicated by new data. As the chairman of this task force, I can attest that the development of the final formulation was an always interesting, often exasperating, and finally quite satisfying experience.<sup>5</sup>

## CHANGES IN TNM CLASSIFICATION OF BREAST CANCER

Note the following differences in the staging of breast cancer between the second and third editions of the *AJCC Manual for Staging of Cancer*:

1. The current formulation has no surgical evaluative stage; therefore, the clinical stage and pathological stage classifications were redefined.

2. The current formulation has no juxtaregional lymph node category; therefore, ipsilateral supraclavicular lymph node metastasis, which was juxtaregional (N3), is now classified as distant (M1).

3. Carcinoma in situ is stage 0 (Tis N0 M0).

4. In the second edition, pathological staging required at least a modified radical mastectomy (the entire breast and all three levels of axillary lymph nodes). In the third edition, pathological staging can be done if the primary cancer is removed with no gross tumor in the margins and, in addition, at least the lowest level (I) of axillary lymph nodes is resected. This redefinition was done so that the increasing numbers of patients treated by breast-conserving pro-

cedures (eg, primary radiation therapy) can be staged pathologically.

5. Classification of the primary tumor (T) has been changed in the following ways:

a. Fixation to the pectoral fascia is not recorded, since its presence or absence does not influence staging.

b. In the second edition, inflammatory carcinoma was considered separately. In the third edition, inflammatory carcinoma is classified T4d.

c. In the second edition, T3 N0 M0 (a tumor more than 5 cm in greatest dimension with no regional or distant metastases) was classified stage IIIA. Based on survival data from the SEER program, the five-year survival rate for T3 N0 M0 (76%) is more closely aligned with stage II (75%) than stage IIIA (56%). Therefore, T3 N0 M0 is now classified stage IIB.

Clarifications have been made in the AJCC and UICC new editions in response to questions received after the publication of the previous editions. Intramammary lymph nodes are considered axillary for classification purposes. The measurement used for clinical classification of the primary tumor (cT) is the one judged most accurate (eg, physical examination or mammogram). The tumor size for pathological classification (pT) is a measurement of the invasive component. For example, if there is a large in situ component (eg, 4.0 cm) and a small invasive component (eg, 0.5 cm), the tumor is classified T1a, as though its total extent were 0.5 cm. When there are multiple simultaneous *ipsilateral* primary carcinomas, the measurement of only the largest is used for classification (T). However, simultaneous *bilateral* breast carcinomas are staged separately as independent primary carcinomas.

I must confess, as the chairman of both the AJCC and the Breast Task Force, that I was somewhat chagrined by the reaction in certain quarters when we initially eliminated the words *movable* and *fixed* from the definitions in the classification of regional (axillary) lymph nodes (N). We went through two generations of modifications of the N categories. These were field tested by feeding them back through the system. An immediate response was received from the Breast Cancer Cooperative Group I of the European Organization for Research on Treatment of Cancer (personal communications, June 11 and Nov 11, 1986). It became quite evident that clinicians throughout Europe have satisfactorily used *movable* and *fixed* in the clinical evaluation of the axilla and are very reluctant to change. Essentially, they adopted the position stated in an old American aphorism, if it ain't broke, don't fix it. So, as a result, the only anatomic sites in which these words appear are the breast, vulva, and larynx. The FIGO also uses these terms to classify metastases to regional lymph nodes from cancer of the vulva. The FIGO liaison representative was not authorized to make such a change without full committee approval, which would have been too late for our editors. However, the problem will be addressed in the future.

## REVISED CLASSIFICATION AND STAGING FOR CARCINOMA OF THE BREAST

The following TNM definitions and stage groupings for carcinoma of the breast are the same for the AJCC<sup>5</sup> and the UICC/TNM Project. This staging system for carcinoma of the breast applies to infiltrating and *in situ* carcinomas. Microscopic confirmation of the diagnosis is mandatory and the histologic type of carcinoma should be recorded.

### Anatomy (ICD-0 174)

**Primary Site.**—The mammary gland, situated on the anterior chest wall, is composed of glandular tissue within a

Stage Groupings			
Stage	Classification		
	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
IIA	T0	N1	M0
	T1	N1*	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1, N2	M0
IIIB	T4	Any N	M0
	Any T	N3	M0
IV	Any T	Any N	M1

\*The prognosis for patients with classification N1a is similar to that for patients with classification N0.

dense fibroareolar stroma. The glandular tissue consists of approximately 20 lobes, each of which terminates in a separate excretory duct in the nipple.

**Regional Lymph Nodes.**—The breast lymphatics drain by way of three major routes: axillary, transpectoral, and internal mammary. Intramammary lymph nodes are considered axillary for staging purposes. Metastases to any other lymph nodes are considered distant (M1) including supraclavicular, cervical, or contralateral internal mammary.

**Metastatic Sites.**—All distant visceral sites are potential sites of metastases. While the four major sites of involvement are bone, lung, brain, and liver, this widely metastasizing disease has been found in almost any remote site.

### Rules for Classification

**Clinical Staging.**—Clinical Staging includes the following: physical examination, including careful inspection and palpation of the skin, mammary gland, and lymph nodes (axillary, supraclavicular, and cervical) and pathologic examination of the breast or other tissues to establish the diagnosis of breast carcinoma. The extent of tissues examined pathologically for clinical staging is less than that required for pathological staging (please see **Pathological Staging** below). Appropriate operative findings are elements of clinical staging, including the following: size of the primary tumor and chest wall invasion, the presence or absence of regional or distant metastasis.

**Pathological Staging.**—Pathological Staging includes the following:

1. All data used for clinical staging.
2. Surgical resection and pathological examination of:
  - a. The primary carcinoma including not less than excision of the primary carcinoma with no tumor in any margin of resection by gross pathological examination. A case can be included in the pathological stage if there is only microscopic, but not gross, involvement at the margin. If there is tumor in the margin of resection by gross examination, it is coded Tx.
  - b. Resection of at least the low axillary lymph nodes (Level I), e.g. those lymph nodes located lateral to the lateral border of the pectoralis minor muscle. Such a resection will ordinarily include six or more lymph nodes.

### TNM Classification

**Primary Tumor (T).**—The clinical measurement used for classifying the primary tumor (T) should be the one judged most accurate (e.g. physical examination or mammogram). Pathologically the tumor size for classification (T) is a measurement of the invasive component. For example, if there is a large *in situ* component (e.g. 4.0 cm) and a small invasive component (e.g. 0.5 cm) the tumor is classified T1a. The size of the primary tumor should be measured before any tissue is removed for special studies, such as for estrogen receptors.

**Multiple Simultaneous Ipsilateral Primary Cancers.**—The following guidelines should be used when classifying multiple simultaneous ipsilateral primary (infiltrating, grossly measurable) carcinomas. These criteria do not apply to one grossly detected tumor associated with multiple separate microscopic foci.

1. Use the largest primary carcinoma to classify T.
2. Enter into the record that this is a case of multiple simultaneous ipsilateral primary carcinomas. Such cases should be analyzed separately.

**Simultaneous Bilateral Breast Carcinomas.**—Each carcinoma should be staged separately.

**Inflammatory Carcinoma.**—Inflammatory carcinoma is a clinicopathologic entity characterized by diffuse brawny induration of the skin of the breast with an erysipeloid edge, usually without an underlying palpable mass. Radiologically there may be a detectable mass and characteristic thickening of the skin over the breast. This clinical presentation is due to tumor embolization of dermal lymphatics. The tumor of inflammatory carcinoma is classified T4d.

**Paget's Disease of the Nipple.**—Paget's disease of the nipple without an associated tumor mass (clinical) or invasive carcinoma (pathological) is classified Tis. Paget's disease with a demonstrable mass (clinical) or an invasive component (pathological) is classified according to the size of the tumor mass or invasive component.

**Skin of Breast.**—Dimpling of the skin, nipple retraction, or any other skin change except those described under inflammatory carcinoma (T4b) may occur in T1, T2, or T3 without changing the classification.

### T Classification

Definitions for classifying the primary tumor (T) are the same for clinical and for pathological classification. The "telescoping" method of classification can be applied. If the measurement is made by physical examination, the examiner will use the major headings (e.g. T1 or T2 or T3). If other measurements, such as mammographic or pathologic, are used the (telescoped) subsets of T1 can be used.

- Tx. Primary tumor cannot be assessed.
- T0. No evidence of primary tumor.
- Tis. Carcinoma in situ: Clinical Paget's disease of the nipple with no tumor mass. Pathological intraductal carcinoma, lobular carcinoma in situ, or Paget's disease with no invasive component.
  - T1. Tumor 2.0 cm or less in greatest dimension.
    - T1a. 0.5 cm or less in greatest dimension.
    - T1b. More than 0.5 cm but not more than 1.0 cm in greatest dimension.
    - T1c. More than 1.0 cm but not more than 2.0 cm in greatest dimension.
  - T2. Tumor more than 2.0 cm but not more than 5.0 cm in greatest dimension.
  - T3. Tumor more than 5.0 cm in greatest dimension.
  - T4. Tumor of any size with direct extension to chest wall or skin. Chest wall includes ribs, intercostal muscles, and

serratus anterior muscle but not pectoral muscle.

T4a. Extension to chest wall.

T4b. Edema (including peau d'orange), or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast.

T4c. Both a and b above.

T4d. Inflammatory carcinoma (please see definition of inflammatory carcinoma in the introduction).

### N—Clinical Classification

Nx. Regional lymph nodes cannot be assessed (e.g. previously removed).

N0. No regional lymph node metastasis.

N1. Metastasis to movable ipsilateral axillary lymph node(s).

N2. Metastases to ipsilateral axillary lymph nodes fixed to one another or to other structures.

N3. Metastasis to ipsilateral internal mammary lymph node(s).

### pN—Pathological Classification

pNx. Regional lymph nodes cannot be assessed (e.g. previously removed or not removed for pathological study).

pN0. No regional lymph node metastasis.

pN1. Metastasis to movable ipsilateral axillary lymph node(s).

pN1a. Only micrometastasis (none larger than 0.2 cm).

pN1b. Metastasis to lymph node(s), any larger than 0.2 cm.

pN1bi. Metastasis in one to three lymph nodes, any more than 0.2 cm and all less than 2.0 cm in greatest dimension.

pN1bii. Metastasis to four or more lymph nodes, any more than 0.2 cm and all less than 2.0 cm in greatest dimension.

pN1biii. Extension of tumor beyond the capsule of a lymph node metastasis less than 2.0 cm in greatest dimension.

pN1biv. Metastasis to a lymph node 2.0 cm or more in greatest dimension.

pN2. Metastasis to ipsilateral axillary lymph nodes that are fixed to one another or to other structures.

pN3. Metastasis to ipsilateral internal mammary lymph node(s).

### M—Distant Metastasis

Mx. Presence of distant metastasis cannot be assessed.

M0. No distant metastasis.

M1. Distant metastasis (includes metastasis to ipsilateral supraclavicular lymph node[s]).

### G—Histopathological Grading

Gx. Grade of differentiation cannot be assessed.

G1. Well differentiated.

G2. Moderately differentiated.

G3. Poorly differentiated.

G4. Undifferentiated.

### Stage Grouping

For stage groupings, see the Table.

### CONCLUSION

It is clearly evident to all who have been involved that international agreement on the classification of cancer at all anatomic sites is exhilarating, since data from around the world can finally be compared with validity. However, our work is not finished. There is room for improvement at some sites. An international group has already agreed to continue to work on improving the classification of brain tumors. There are sites for which we currently have no system of classification, such as the small bowel, gastrointestinal carcinoids, visceral sarcomas, and hepatic and pulmonary metastases; these are currently being addressed. Finally, now that universal agreement has been reached on a classification based on anatomic extent of disease, we must question whether such a classification is too restrictive. Other elements may also be important, such as biologic markers as evidence of distant spread and duration of symptoms as an indicator of biologic aggressiveness.

While we have come a long way and appreciate that the changes made were necessary for improvement and international agreement, we are also very sensitive to the need for cancer registries to have a stable format for the acquisition of data without change for long periods of time. It is our hope that this newly modified TNM system will provide such stability and will be changed only as required by significant new scientific evidence.

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### In Other AMA Journals

#### ARCHIVES OF INTERNAL MEDICINE

#### Nephrotoxicity of Common Drugs Used in Clinical Practice

Kerry Cooper, MD, William M. Bennett, MD

Drug-induced nephrotoxicity is an increasingly recognized complication of a wide variety of therapeutic agents. The nephrotoxicity of three of the most commonly used drug groups are reviewed in this article. They include antibiotics, radiocontrast agents, and nonsteroidal anti-inflammatory drugs. Since the clinical spectrum of drug-induced nephrotoxicity is broad, it is imperative that the clinician recognize these nephrotoxic syndromes while they are reversible with discontinuation of the offending drug (*Arch Intern Med* 1987;147:1213-1218).

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