The Staging of Cancer: A Retrospective and Prospective Appraisal

Frederick L. Greene, MD; Leslie H. Sobin, MD

ABSTRACT The tumor-node-metastasis (TNM) classification describes the anatomic extent of cancer. The ability to separately classify the individual T, N, and M elements and then group them into stages differs from other cancer staging classifications, which are primarily concerned with summarized groups. The objectives of the TNM system are to aid clinicians and investigators in planning treatment, assessing prognosis, stratifying patients for therapeutic studies, evaluating the results of treatment, and facilitating communication. The most important challenge facing TNM is how to interface the current taxonomy with the numerous nonanatomic prognostic factors currently in use or under study. As nonanatomic prognostic factors become widely used, TNM will remain a solid foundation on which to build prognostic classifications. There is, however, a risk that this system will be corrupted by a variety of irrelevant prognostic data. An anatomic extent of disease classification is needed to provide a standard against which to measure the importance of nonanatomic factors. Methods are needed to express overall prognosis without losing the vital anatomic content of TNM. These methods should be able to integrate multiple prognostic factors, including TNM, yet permit TNM to remain intact and distinct. (CA Cancer J Clin 2008;58:180–190.) © American Cancer Society, Inc., 2008.

Disease is very old and nothing about it has changed. It is we who change, as we learn what was formerly imperceptible.
—Jean-Martin Charcot, De L’Expectation en Médecine

INTRODUCTION

The anatomic extent of disease is one of the 3 main axes of tumor classification, the others being topographic site and histological type.

Staging provides a format for the uniform exchange of information among clinicians regarding extent of disease and a basis for their selection of initial therapeutic approaches and consideration of the possible need for adjuvant treatment. For clinical investigators, staging allows the stratification of patients in observational and interventional therapeutic studies and facilitates the exchange of information through data sets and peer-reviewed communication. Staging provides a means to evaluate nonanatomic prognostic factors at specific anatomic stages. For example, microsatellite instability in sporadic colon cancer is associated with improved prognosis, but this appears to apply to Stages III and IV but not Stages I and II carcinomas (Figure 1). Staging can also be used to measure early detection efforts (eg, to see what impact screening could have on the stage distribution of disease at the time of diagnosis).

HISTORY OF CANCER STAGING

Staging of cancer started over a hundred years ago. The efforts were focused on specific anatomic sites of cancer. The system advocated by Dukes for rectal cancer is an example. The first effort to develop a staging system whose

Disclosures: The authors have no financial relationship with any products or publications discussed in this article. The opinions and assertions contained herein are the expressed views of the author and are not to be construed as official or reflecting the views of the Departments of the Army or Defense.
principles and codes could be applied to all cancer sites was that of the French surgeon Pierre Denoix, who between 1943 and 1952 developed the tumor-node-metastasis (TNM) classification.\(^3\) In 1958, the first international TNM recommendations were published by the International Union Against Cancer (UICC) for the clinical stage classification of cancers of the breast and larynx.\(^4\) Between 1960 and 1967, 9 UICC brochures were published describing proposals for the classification of tumors at 23 body sites. In 1968, these brochures were combined, representing the First Edition of TNM.\(^5\) In 1974 and 1978, Second and Third Editions\(^6,7\) appeared containing new site classifications and amendments to previously published classifications. The Third Edition was enlarged and revised in 1982.

Over the years, variations in the rules of classification of certain sites were introduced. In order to achieve standardization, in 1982, the national TNM committees agreed to formulate a single TNM classification. A series of meetings was held to unify and update existing classifications, as well as to develop new ones. The result was the Fourth Edition of TNM, coordinated with the UICC and American Joint Committee on Cancer (AJCC) and representing the achievement of a worldwide agreement for the staging of adult solid tumors.\(^8\) Each subsequent edition of the TNM classification was accompanied by an illustrated TNM Atlas,\(^9,10\) which graphically depicts the T and N categories.

In 1993, the UICC’s TNM project published the TNM Supplement.\(^11\) Its purpose was to promote the uniform use of TNM by providing detailed explanations of the TNM rules with practical examples. It also included proposals for new classifications and optional expansions of selected categories. In 1995, the project published Prognostic Factors in Cancer,\(^12\) a compilation and discussion of prognostic factors in cancer at each of the body sites. This was updated in 2002 and 2006 with Second and Third Editions.\(^13,14\)

Since the Fourth Edition, the TNM classification of the UICC and that of the AJCC have been identical, owing to the close cooperation and communication between these 2 bodies. Thus, the present (Sixth) UICC edition of TNM\(^15\) contains

---

**FIGURE 1** Effect of Microsatellite Instability on Survival of Colon Cancer Patients. Microsatellite instability in sporadic colon cancer is associated with improved prognosis. Reprinted from Samowitz WS, Curtin K, Ma KN, et al\(^{1}\) with permission from Cancer Epidemiol Biomarkers Prev.
rules of classification and staging that correspond exactly with those of the Sixth Edition of the AJCC Cancer Staging Manual. TNM now appears in over a dozen translations and is available online.

Currently, there have been 6 editions of both the UICC and AJCC publications. Plans are currently being made for a Seventh Edition, which will be published in the spring of 2009 and will be used for patients diagnosed after January 1, 2010. The development of these staging strategies depends on new data that have been derived from large data sets and from the peer-reviewed literature. Groups of experts have been assigned to each specific tumor site and have made decisions relative to the inclusion of new anatomic markers and molecular or serum markers that have been introduced into the management strategies for a variety of tumors.

THE PRINCIPLES OF TNM

Classification

The TNM classification describes the anatomic extent of cancer and is based on the premise that the choice of treatment and the chance of survival are related to the extent of the tumor at the primary site (T), the presence or absence of tumor in regional lymph nodes (N), and the presence or absence of metastasis beyond the regional lymph nodes (M). Tumors must be classified before treatment (ie, clinical staging [cTNM]) and after surgical intervention (ie, pathologic staging [pTNM]). T is usually divided into 4 major parts (T1 to T4), expressing increasing size or spread of the primary tumor. N and M comprise at least 2 categories each (0 and 1—absence or presence of tumor). A number of sites have subcategories, with up to 4 subdivisions of T1 and T4 and 6 subdivisions of pN1 in breast carcinoma and 3 subdivisions of M in prostate carcinoma.

Stage Grouping

Classification by the TNM system achieves a reasonably precise description and recording of the apparent anatomic extent of disease. However, a tumor with 4 degrees of T, 3 degrees of N, and 2 degrees of M will have 24 TNM categories. For purposes of tabulation and analysis, except in very large series, it is necessary to condense these categories into a convenient number of TNM stage groups. The grouping adopted must ensure that each group is homogeneous with respect to survival and that the survival rates of these groups for each cancer site are distinctive (eg, patients with Stage I tumors usually survive their disease; those with Stage IV usually succumb to the disease). The TNM system's ability to separately classify the individual elements and then group them into stages differs from other cancer staging classifications, which are primarily concerned with the summarized groups (eg, Dukes A, B, C).

Pediatric tumors are not included in this staging strategy. Tumors of the female reproductive system are clinically and pathologically staged by the classification of the International Federation of Gynecology and Obstetrics. In each TNM edition, they have been converted into the TNM system.

STAGING AS A CLINICAL TOOL

The importance of staging cannot be overemphasized in the management of patients. A primary role for staging is to stratify patients into groups that are prognostically and therapeutically similar. Without this framework, it would be difficult to have any meaningful clinical trials. A second goal for staging is that it allows for comparison across large populations either within geopolitical borders or between disparate countries. Because the current anatomic (TNM) staging strategy is worldwide, this opportunity for comparison becomes even more important.

Thirdly, staging allows a framework for discussion, especially among physicians who care for the individual patient. Staging in fact is our “language of cancer,” and it is necessary for that language to be learned early in medical education to allow clinicians to become facile with the dialect and vernacular of staging strategies.

TNM STAGE AND PROGNOSTIC FACTORS

One of the criticisms of the current TNM system is that it may be biologically too simple. We know that generally a tumor will grow locally and expand in a locoregional manner. Following
this local growth, there may or may not be orderly involvement of regional lymph nodes, although the mechanisms of this spread are yet to be fully elucidated. Finally, tumors spread to visceral organs and may or may not involve surrounding lymphovascular structures. The biology of most tumors is certainly more complex than this simple framework, although the basis of the TNM system has stood the test of time. Basic TNM elements and the combination of these elements (stage group) serve as one of the most important prognostic factors in making assumptions relative to the overall survival of the cancer patient. One definition of a prognostic factor is that it "serves as a variable that can explain some of the heterogeneity associated with the expected course and outcome of a disease."19 This factor has a role in foretelling the future of the specific cancer patient but must be modified and modulated by other important biological factors that are currently being assessed.

One of the difficulties in creating the current anatomic TNM system is to review and rank all of the variable prognostic factors that have been published for a given site of cancer. In developing the Sixth Edition of the AJCC Cancer Staging Manual,16 at least 80 prognostic factors for breast cancer were identified and assessed for their importance in the survival of patients with breast cancer. The strategy is to apply well-tested, evidence-based methodology to each factor to assess the significance and statistical power before applying the specific factor to the TNM lexicon. The traditional prognostic parameters for human breast cancer have stood the test of time and currently include specific tumor factors of size, lymph node status, and grade of tumor. Other important factors, such as lymphatic and vascular invasion and hormonal markers (estrogen or progesterone receptors), are certainly relevant but have not yet been added to the official TNM staging system for breast cancer. Additional factors such as DNA content (ploidy, s-phase fraction) have been considered important but as yet have not been added to TNM.

Along with tumor factors, it is important to consider factors specific for the individual patient or host. The patient’s age and menopausal status have, of course, been shown to be important as they specifically relate to the role of hormonal markers. Currently, the only site for anatomic staging that includes age as a specific staging factor is thyroid cancer, which indicates that patients under the age of 45 years have a less aggressive form of their disease. In addition to the host factors of age and reproductive history, familial history and molecular factors (eg, microsatellite instability) will continue to be important as prognostic factors but have not yet been added to traditional TNM. Other factors, such as immune status and obesity, also have a role to play in the prognosis of some forms of cancer. It is presumed that these 2 factors will be added to conventional anatomic staging as methodology improves to stratify patients with both immune and nutritional issues.

NEW CONCEPTS IN N CLASSIFICATION

The role of nodal and lymphovascular involvement cannot be overemphasized in the prognosis and staging of many solid tumors. Current strategies have included the number of tumor-containing nodes in the locoregional area, as well as the volume of tumor contained in these nodal elements. Strategies to stage breast cancer and decisions for treatment of breast cancer are directly related to the microscopic involvement of lymph nodes in the axillary region. One of the important issues is to stratify nodes either into regional or distant sites and to address the issue of whether nodal involvement in a distant site is more important than locoregional nodal positivity. These decisions are especially important since clinical trials may well be based on the inclusion only of patients with locoregional disease while excluding patients with node positivity in distant sites. This became especially pertinent in women with breast cancer who had supraclavicular nodal disease. In the Fifth Edition of the AJCC and UICC staging strategies,20,21 these women were classified as having M1 or Stage IV breast cancer. Review of larger data sets, however, showed that women with supraclavicular metastatic disease had the same survival as women with multiple axillary nodes involved. These patients should not be designated as Stage IV based on supraclavicular disease alone. Since 2002, patients having supraclavicular nodal metastases have now been reclassified as having N3 disease and, most
importantly, are judged appropriate for clinical trials dealing with locoregional disease alone.

**N Staging in the Era of Sentinel Node Mapping**

In the era of sentinel node evaluation, it has become especially appropriate to develop language within the TNM system that will allow for other nodal areas to be included, such as the internal mammary chain. While these nodes are generally not assessed pathologically, they may be evaluated clinically using modern computed tomography-positron emission tomography studies and, therefore, should be included in the cTNM of the TNM staging strategy. The finding of positivity in the internal mammary chain is especially relevant during discussion of radiation fields as an adjunct to mastectomy and chemotherapy in the breast cancer patient. Studies have shown that internal mammary positivity may be a worse prognostic factor and should be assessed using sentinel node technology.

It is important in the recording of both clinical and pathological data relative to patients having sentinel node evaluation that there is a descriptor indicating that the sentinel node may be the only nodal entity examined. With this in mind, the suffix (sn) has been introduced to indicate that the lymph node, whether negative or positive, is a sentinel node only and does not indicate a node from a complete axillary or regional dissection. With the introduction of sentinel node evaluation in breast cancer, melanoma, head and neck cancer, and several GI sites, the importance of designating specific nodes in data collections is becoming more critical.

The assessment of nodal disease in staging strategies should not be taken out of context but always should be associated with other variables relative to specific tumors. An example of this is melanoma of the skin in which thickness and ulceration of melanoma are specific and independent prognostic factors. The mitotic rate of the primary melanoma has also been found to have some important significance in prognosis and will most likely be included as a specific factor in staging of melanoma in the *Seventh Edition* of TNM. The important issue is that the thickness of the melanoma (Breslow classification) and the appearance of microscopic ulceration are both surrogates of nodal involvement and metastatic behavior. As is true in breast cancer, the number of nodes involved with melanoma becomes an important prognostic variable. In addition to microscopic involvement of nodes, macroscopic nodal involvement indicated by clinical palpation is an important factor. Survival patterns in melanoma generally worsen as the number of nodes involved increases in the locoregional draining areas of the primary melanoma. The total staging strategy of melanoma, which depends on the thickness, ulceration, and nodal involvement, creates a dynamic staging strategy indicating that patients with nonulcerated melanoma with microscopic involvement of one node have a 63% 10-year survival, whereas those with ulcerated melanoma and greater than 4 macroscopic (clinically palpable) nodes have an 8% 10-year survival (Table 1). Because of the capricious nature of melanoma, cure rates in this disease cannot be considered in the traditional 5- or 10-year timeframe. Death resulting from melanoma continues to 15 years or more and is based on the biology of the tumor (Figure 2). This is another example of the intertwining of overall cancer biology with traditional TNM anatomic staging.

### Isolated Tumor Cells

An additional biological parameter is the concept of finding isolated tumor cells (ITC) in lymph nodes. In contrast to micrometastases, which are cell clusters at least 0.2 mm but no

| Microscopic Nodes Positive | Macroscopic Nodes Positive |
|---------------------------|----------------------------|
| Primary                   | 1                          |
| No ulceration             | 63%                        |
| Ulceration                | 38%                        |
| 2 to 3                    | 57%                        |
| ≥4                        | 14%                        |
| 1                         | 48%                        |
| 2 to 3                    | 38%                        |
| ≥4                        | 16%                        |
| 1                         | 24%                        |
| 2 to 3                    | 15%                        |
| ≥4                        | 8%                         |

TABLE 1 Diversity of Stage III Melanoma: Ten-year Survival
larger than 2 mm in greatest diameter, ITC are defined as a cell or cluster of cells less than or equal to 0.2 mm in greatest diameter.\textsuperscript{24,25} These ITC are indicated by the suffix (i+) or (i−), which is related to the specific nodes under study. Because of developments in immunohistochemistry, smaller and smaller tumor deposits have been identified in the subcapsular and parenchymal regions of draining nodes. The finding of ITC becomes extremely important when sentinel nodes are being evaluated that may only contain these small foci of cancer. For the purpose of classification, ITC was originally defined as a single cell or small cluster of cells.\textsuperscript{24} The measurement of “less than or equal to 0.2 mm” was later introduced to limit the size of the process when multiple sites of small clusters are identified in the same lymph node; this may have a much different prognostic implication, and current opinions favor avoiding specific size constraints of the individual clusters when dealing with ITC (L. H. Sobin, F. L. Greene, C. Wittekind, D. Page, unpublished data, 2008) (Figures 3 and 4). The implication for treatment when only ITC are found in lymph nodes is important, especially since traditional TNM staging continues to define this category of nodal involvement as N0. There is evidence indicating that ITC in the absence of nodal micro- or macrometastases may have adverse prognostic significance in melanoma.\textsuperscript{26} The ITC concept will probably become more important as earlier-stage disease is found and more aggressive sentinel node examination is undertaken.

**Molecular Ultrastaging**

While it is difficult for medical oncologists to recommend against systemic chemotherapy when ITC have been found in a patient’s regional nodal bed, it is important that clinical trials be developed that will answer the questions relative to the prognostic implication of minimal nodal positivity. This is especially true in the era of molecular diagnostics in which polymerase chain reaction (PCR), reverse transcriptase PCR, and other methods for analysis of nucleic acids become more commonly used. This molecular staging strategy has necessitated the creation of a suffix (mol) that indicates either a positive or negative finding in the lymph node when PCR is applied. It is anticipated that most institutions in the future will have the technology to easily perform molecular diagnostic testing on nodal
tissue. This approach has now been introduced for the intraoperative assessment of sentinel nodes in the management and decision making for breast cancer.27

Previous iterations of the TNM system tended to lump patients with nodal positivity into broadly defined staging groups. This was especially evident in the classification of colorectal cancer where patients with positive mesenteric nodes were stratified to a common group collectively designated as Stage III. Using large data sets provided by the National Cancer Data Base, it became evident that 3 specific subsets of patients could be defined based on depth of penetration of the primary tumor into the wall of the bowel and the number of nodes found to be positive in the mesentery.28 These 3 subsets, defined as Stages IIIA (T1 to 2, N1), IIIB (T3 to 4, N1), and IIIC (any T, N2), showed 3 characteristic and distinct survival curves (Figure 5). The implication is important in that it may mean that the Stage IIIA patient should be treated in a different fashion and with different chemotherapeutic agents than the Stage IIIC patient. Currently, most patients with node-positive colon cancer receive similar chemotherapeutic agents, and the treatment stratification according to subsets of Stage III disease has not been instituted.29

Completeness of Nodal Sampling

The corollary to the staging of colon cancer is that an adequate number of nodes must be resected by the surgeon and investigated by the pathologist in order to adequately assess each patient. Current data suggest that there is a more favorable outcome for patients based on the ability to resect and identify a greater number of nodes, regardless of pathological findings (Figure 6). The ratio of positive to total nodes resected is also being studied and may be an important prognostic factor in gastrointestinal as well as other sites. The total number of nodes resected may have an even greater benefit in Stage II patients in which positive nodes have not been identified.30 This has become apparent by examining a large group of Stage II patients reported in the National Cancer Data Base (Figure 6). The number of nodes resected in colon cancer is currently being used as a benchmark of quality for both surgeons and pathologists and will ultimately have implications for payment strategies to individual practitioners as well as institutions. A recently published study31 refutes the concept that greater nodal evaluation (12 or more nodes) in colon cancer patients should be used as a quality indicator in hospitals. At the individual patient level, however, increasing nodal evaluation remained a strong prognostic factor for survival, especially in Stage II disease.

There are other sites included in TNM anatomic staging that account for nodal assessment but that do not fit easily into the strategies previously described in breast cancer, melanoma, and colorectal cancer. One of these is soft tissue sarcoma in which nodal involvement is an uncommon finding and has a graver prognostic implication when found. Specific histological types of sarcomas may commonly involve regional nodes.32 Any nodal involvement in sarcoma is considered to be similar to visceral metastatic disease and, therefore, is given a Stage IV designation.
biology of sarcoma is much more dependent on histological grade and whether the location is superficial or deep, especially in the types of sarcoma in which nodal disease is not a frequent characteristic.

Unlike sarcoma, in differentiated thyroid cancer (papillary or follicular), nodal involvement may have a very benign course. While it is becoming more fashionable to resect nodes in the management of differentiated thyroid cancer, large data sets show that nodal positivity may be associated with significant long-term survival.33 As stated previously, the age of the patient and the primary histological variant of tumors of the thyroid are more important as prognostic factors than even nodal involvement. Specific areas in the neck, especially the central region (level VI), should be assessed in the management of thyroid tumors.34 Specific nodal levels in head and neck cancer have prognostic implication, especially with tumors of the oropharynx and larynx.35 Traditionally, these nodal sites have been resected during radical procedures for head and neck tumors. These regional nodal beds are also used as diagnostic clues for localization in patients who have occult tumors of the head and neck.

**THE FUTURE**

The most important challenge facing the TNM classification is how to interface with the great number of nonanatomic prognostic factors that are currently in use or under study, as illustrated in Table 2. TNM was constructed to assess only the 3 basic facets of anatomic spread. However, at certain sites (soft tissues, bone, prostate), histologic grading became incorporated into the stage groups. More recently, serum factors have become part of the stage grouping for testis and gestational trophoblastic tumors. It is inevitable

---

**TABLE 2** Selected Essential, Additional, and New and Promising Prognostic Factors for Colorectal Carcinoma37

| Essential factors | T, N, M categories |
|-------------------|--------------------|
|                   | Histologic grade   |
|                   | Extramural venous invasion |
|                   | Obstruction         |
|                   | Quality of surgery  |

| Additional factors | Grade |
|--------------------|-------|
|                    | Tumor perforation |
|                    | Perineural invasion |
|                    | Invasive pattern  |
|                    | Peritumoral lymphoid reaction |
|                    | Medullary type    |
|                    | CEA serum level   |
|                    | Number of lymph nodes resected |

| New and promising factors | Microsatellite instability |
|---------------------------|---------------------------|
|                           | LOH 18q status |
|                           | P53 |
|                           | DNA ploidy |
|                           | VEGF expression |
|                           | 20q copy number |
|                           | Karyotype |
|                           | (and others) |

Abbreviations: T, extent of the tumor at the primary site; N, the presence or absence of tumor in regional lymph nodes; M, the presence or absence of metastasis beyond the regional lymph nodes; CEA, carcinoembryonic antigen; LOH, loss of heterozygosity; VEGF, vascular endothelial growth factor.

**TABLE 3** TNM Stage Grouping of Colorectal Carcinoma15,16

| Stage | Tumor | Node | Metastasis |
|-------|-------|------|------------|
| Stage 0 | Tis | N0 | M0 |
| Stage I | T1 | N0 | M0 |
| Stage II | T2 | N0 | M0 |
| Stage III | Any T | N1 | M0 |
| Stage IV | Any T | Any N | M1 |

Stage groups include only TNM elements. Abbreviation: TNM, tumor-node-metastasis.

**TABLE 4** TNM Stage Grouping of Soft Tissue Sarcomas15,16

| Stage | Tumor | Node | Metastasis | Grade |
|-------|-------|------|------------|-------|
| Stage IA | T1a | N0 | M0 | G1, 2 |
| Stage IB | T1b | N0 | M0 | G1, 2 |
| Stage IIA | T2a | N0 | M0 | G1, 2 |
| Stage IIB | T2b | N0 | M0 | G3, 4 |
| Stage IIC | T1a | N0 | M0 | G3, 4 |
| Stage III | T1b | N0 | M0 | G3, 4 |
| Stage IV | Any T | N1 | M0 | Any G |
|          | Any T | Any N | M1 | Any G |

Stage groups include histologic grade, as well as T, N, and M. Abbreviation: TNM, tumor-node-metastasis.
that additional nonanatomic factors will be added to these and other sites in the future. The challenge for those directing these future staging strategies is to incorporate these factors without affecting or minimizing the importance of anatomic staging. Tables 3, 4, and 5 illustrate the increasing complexity of stage grouping when factors other than T, N, and M are included.

As nonanatomic prognostic factors become widely used, TNM provides an inviting foundation on which to build a prognostic classification. Even if certain nonanatomic factors were shown to be of greater importance than anatomic extent, an anatomic extent of disease classification would be needed to evaluate nonanatomic prognostic factors at specific anatomic stages and compare the weight of nonanatomic factors with extent of disease factors. Therefore, other methods should be explored to help express overall prognosis without losing the vital anatomic content of TNM.

Artificial neural networks, nomograms, site-specific prognostic classifications, etc. (Table 6) offer the potential of integrating numerous and diverse prognostic factors, anatomic and nonanatomic, into a system that could go beyond conventional staging to enhance the prediction of survival.

---

**TABLE 5**  TNM Stage Grouping of Germ Cell Tumors of the Testis\(^{15,16}\)

| Stage     | Tumor Node Metastasis | Serum Factor |
|-----------|----------------------|--------------|
| Stage 0   | pTis N0 M0 SX        | S0, SX       |
| Stage 1   | pT1 to 4 N0 M0 SX    | SX           |
| Stage 1A  | pT1 N0 M0 SX         | S0           |
| Stage 1B  | pT2 N0 M0 SX         | S0           |
| Stage 1C  | pT3 N0 M0 SX         | S0           |
| Stage IS  | Any pT/TX N0 M0 SX   | S1 to 3      |
| Stage II  | Any pT/TX N1 to 3 M0 | SX           |
| Stage IIA | Any pT/TX N1 M0 SX   | S0           |
| Stage IIB | Any pT/TX N2 M0 SX   | S0           |
| Stage IIC | Any pT/TX N3 M0 SX   | S0           |
| Stage III | Any pT/TX Any N M1, M1a SX | S1 |
| Stage IIIA| Any pT/TX Any N M1 M1a SX | S0 |
| Stage IIIB| Any pT/TX N1 to 3 M0 | S2           |
| Stage IIIC| Any pT/TX Any N M1 M1a S0 | S3 |

Stage groups include serum factors, as well as T, N, and M. Abbreviation: TNM, tumor-node-metastasis.

**TABLE 6**  Weight of the Six Prognostic Factors in the Chinese University Prognostic Index for Liver Carcinoma. A Site-specific Prognostic Classification that Incorporates Anatomic and Nonanatomic Factors

| Variable               | Weight (CUPI Score) |
|------------------------|---------------------|
| TNM stage              |                     |
| Stage I and II         | –3                  |
| Stage III              | –1                  |
| Stage IV               | 0                   |
| Asymptomatic disease   | –4                  |
| Ascites                | 3                   |
| AFP ≥500 ng/mL         | 2                   |
| TB (µmol/L)            |                     |
| <34                    | 0                   |
| 34 to 51               | 3                   |
| ≥52                    | 4                   |
| ALP ≥200 IU/L          | 3                   |
| Risk                   | 12-month Survival % |
| Low <1                 | 48                  |
| Intermediate 2 to 7    | 17                  |
| High ≥8                | 5                   |

Abbreviations: TNM, tumor-node-metastasis; CUPI, Chinese University Prognostic Index; AFP, α-fetoprotein; TB, total bilirubin; ALP, alkaline phosphatase. Modified from Leung TW, Tang AM, Zee B, et al\(^{18}\) with permission from Cancer.
outcome, permit treatment to be individualized, and improve cancer patient management. The interrelationship of anatomic factors and molecular markers depends on adding prognostic factors to TNM much as branches and leaves are added to the main tree trunk.

Staging strategies are thus dependent on prognostic factors that involve the primary tumor, the patient, and even the environment as it relates to the opportunities for early treatment and follow-up care. Newer and more specific prognostic factors dealing with molecular diagnostic studies are being introduced into staging strategies. In the future, the traditional anatomic staging will be closely linked with molecular markers. The T, N, and M descriptors, along with other prognostic factors, will be primary data points in nomograms relating to a number of tumor sites. These data elements will be fed into either hand-held or Internet-based sites to give direction for both patients and physicians and to help with decision making relative to the type of multidisciplinary care that is necessary for treatment. All of these together will add up to a prognostic quilt that will have a somewhat different appearance than our traditional anatomic concepts.

The future depends on newer diagnostic methods that are being introduced into pathological assessment and, more importantly, into clinical and preoperative imaging. The traditional dichotomy of cTNM and pTNM must be melded into one continuum and should allow for the interaction of both clinical and pathological elements in our language of staging. All of this will depend on improved data collection and especially the science of medical informatics, which is based on the collection of large data sets. The data acquisition for melanoma and gastrointestinal cancer has been used to refine our traditional staging strategies, and this concept will no doubt be used in other sites as we go forward with the blending of anatomic and molecular markers.

The introduction of artificial intelligence and the unification of concepts within the structure of nomograms will no doubt help to refine the language of cancer and will give a greater acuity of information to physicians, patients, and their caregivers. The one factor that still remains relatively undefined and elusive is the understanding of the individual biology of the tumor. This is the real Holy Grail of staging, and we have yet to comprehend the specific biological factors that will give us the ultimate prognostic information. As Sir William Osler stated in the early 20th century, “Medicine is a science of uncertainty and an art of probability.”

REFERENCES

1. Samowitz WS, Curtin K, Ma KN, et al. Microsatellite instability in sporadic colon cancer is associated with an improved prognosis at the population level. Cancer Epidemiol Biomarkers Prev 2001;10:917–923.
2. Dukes CE. The classification of cancer of the rectum. J Pathol Bacterial 1932;35:323–332.
3. Denoix PF. Nomenclature classification des cancers [in French]. Bull Inst Nat Hyg (Paris) 1952;7:743–748.
4. UICC Committee on Clinical Stage Classification and Applied Statistics. Clinical Stage Classification and Presentation of Results, Malignant Tumours of the Breast and Larynx. Paris, France: International Union Against Cancer; 1958.
5. International Union Against Cancer. TNM Classification of Malignant Tumours. Geneva, Switzerland: International Union Against Cancer; 1968.
6. International Union Against Cancer. TNM Classification of Malignant Tumours. 2nd ed. Geneva, Switzerland: International Union Against Cancer; 1974.
7. Harmer MH, ed. TNM Classification of Malignant Tumours. 3rd ed. Geneva, Switzerland: International Union Against Cancer; 1978. Enlarged and revised 1982.
8. Hutter RV. At last—worldwide agreement on the staging of cancer. Arch Surg 1987;122:1235–1239.
9. Wittekind C, Greene FL, Hutter RV, et al. TNM Atlas: Illustrated Guide to the TNM Classification of Malignant Tumours. 5th ed. Hoboken, NJ: John Wiley & Sons; 2005.
10. Greene FL, Compton CC, Fritz AG, et al. AJCC Cancer Staging Atlas. New York, NY: Springer, Inc.; 2006.
11. Hermanek P, Henson DE, Hutter RV, Sobin LH. International Union Against Cancer (UICC): TNM Supplement 1993. A Commentary on Uniform Use. New York, NY: Springer-Verlag; 1993.
12. Hermanek P, Gospodarowicz MK, Henson DE, et al. International Union Against Cancer (UICC): Prognostic Factors in Cancer. New York, NY: Springer-Verlag; 1995.
13. Gospodarowicz MK, Henson DE, Hutter RV, et al. Prognostic Factors in Cancer. 2nd ed. New York, NY: Wiley-Liss; 2001.
14. Gospodarowicz MK, O’Sullivan B, Sobin LH. Prognostic Factors in Cancer. 3rd ed. New York, NY: Wiley; 2006.
15. Sobin LH, Wittekind C. International Union Against Cancer (UICC) TNM Classification Of Malignant Tumors. 6th ed. New York, NY: Wiley-Liss; 2002.
16. Greene FL, Page DL, Fleming ID, et al. AJCC Cancer Staging Manual. 6th ed. New York, NY: Springer; 2002.
17. TNM Online. Available at: http://www3.inter science.wiley.com/cgi-bin/mrw/home/10455799/HOME. Accessed November 6, 2007.
18. Gospodarowicz MK, Miller D, Groome PA, et al. The process for continuous improvement of the TNM classification. Cancer 2004;100:1–5.
19. Harrington L, Bristow R, Hill RP, Tannock IF. Introduction to cancer biology, in Tannock IF, Hill RP, Bristow R, Harrington L (eds). The Basic Science of Oncology. 4th ed. New York, NY: McGraw Hill; 2005:1–3.
20. Fleming ID, Cooper JS, Henson DE, et al. AJCC Cancer Staging Manual. 5th ed. Philadelphia, PA: Lippincott-Raven; 1997.
21. Sobin LH, Wittekind C. TNM Classification of Malignant Tumours. 5th ed. New York, NY: Wiley-Liss; 1997.

22. Sugg SL, Ferguson DJ, Posner MC, Heimann R. Should internal mammary nodes be sampled in the sentinel lymph node era? Ann Surg Oncol 2000;7:188–192.

23. Ross MI. Early-stage melanoma: staging criteria and prognostic modeling. Clin Cancer Res 2006;12:2312–2319.

24. Hermanek P, Hutter R V, Sobin LH, Wittekind C. International Union Against Cancer. Classification of isolated tumor cells and micrometastasis. Cancer 1999;86:2668–2673.

25. Singleterry E, Greene FL, Sobin LH. Classification of isolated tumor cells: Clarification of the 6th edition of the American Joint Committee on Cancer Staging Manual. Cancer 2003;98:2740–2741.

26. Scheri RP, Issner R, Turner RR, et al. Isolated tumor cells in the sentinel node affect long-term prognosis of patients with melanoma. Ann Surg Oncol 2007;14:2861–2866.

27. Dell’Orto P, Biasi MO, Del Curto B, et al. Assessing the status of axillary sentinel lymph nodes of breast carcinoma patients by a real-time quantitative RT-PCR assay for mammaglobin 1 mRNA. Breast Cancer Res Treat 2006;98:185–190.

28. Greene FL, Stewart AK, Norton HJ. A new TNM staging strategy for node-positive (stage III) colon cancer: an analysis of 50,042 patients. Ann Surg 2002;236:416–421.

29. André T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343–2351.

30. Tsai HL, Lu CY, Hsieh JS, et al. The prognostic significance of total lymph node harvest in patients with T2-4N0M0 colorectal cancer. J Gastrointest Surg 2007;11:660–665.

31. Wong SL, Ji H, Hollenbeck BK, et al. Hospital lymph node examination rates and survival after resection for colon cancer. JAMA 2007;298:2149–2154.

32. Fong Y, Cont DG, Woodruff JM, Brennan MF. Lymph node metastasis from soft tissue sarcoma in adults. Analysis of data from a prospective database of 1772 sarcoma patients. Ann Surg 1993;217:72–77.

33. Cunningham MP, Duda RB, Recant W, et al. Survival discriminants for differentiated thyroid cancer. Am J Surg 1990;160:344–347.

34. Hay ID. Management of patients with low-risk papillary thyroid carcinoma. Endocr Pract 2007;13:521–533.

35. Shah JP, Andersen PE. The impact of patterns of nodal metastasis on modifications of neck dissection. Ann Surg Oncol 1994;1:521–532.

36. Leung TW, Tang AM, Zee B, et al. Construction of the Chinese University Prognostic Index for hepatocellular carcinoma and comparison with the TNM staging system, the Okuda staging system, and the Cancer of the Liver Italian Program staging system: a study based on 926 patients. Cancer 2002;94:1760–1769.

37. Gospodarowicz MK, O’Sullivan B, Koh ES. Prognostic factors: principles and applications, in Gospodarowicz MK, O’Sullivan B, Sobin LH (eds). Prognostic Factors in Cancer. 3rd ed. Hoboken, NJ: John Wiley & Sons; 2006:23–38.

38. White RR, Kattan MW, Haney JC, et al. Evaluation of preoperative therapy for pancreatic cancer using a prognostic nomogram. Ann Surg Oncol 2006;13:1485–1492.

39. Specht MC, Kattan MW, Gonen M, et al. Predicting nonsentinel node status after positive sentinel lymph biopsy for breast cancer: clinicians versus nomogram. Ann Surg Oncol 2005;8:654–659.

40. Bean WB, ed. Sir William Osler: Aphorisms from His Bedside Teachings and Writings. Collected by Robert Bennett Bean, M.D. 3rd ed. Springfield, IL: Charles C. Thomas Co., 1968.