The Eighth Edition AJCC Cancer Staging Manual: Continuing to Build a Bridge From a Population-Based to a More "Personalized" Approach to Cancer Staging

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Abstract: The American Joint Committee on Cancer (AJCC) staging manual has become the benchmark for classifying patients with cancer, defining prognosis, and determining the best treatment approaches. Many view the primary role of the tumor, lymph node, metastasis (TNM) system as that of a standardized classification system for evaluating cancer at a population level in terms of the extent of disease, both at initial presentation and after surgical treatment, and the overall impact of improvements in cancer treatment. The rapid evolution of knowledge in cancer biology and the discovery and validation of biologic factors that predict cancer outcome and response to treatment with better accuracy have led some cancer experts to question the utility of a TNM-based approach in clinical care at an individualized patient level. In the Eighth Edition of the *AJCC Cancer Staging Manual*, the goal of including relevant, nonanatomic (including molecular) factors has been foremost, although changes are made only when there is strong evidence for inclusion. The editorial board viewed this iteration as a proactive effort to continue to build the important bridge from a "population-based" to a more "personalized" approach to patient classification, one that forms the conceptual framework and foundation of cancer staging in the era of precision molecular oncology. The AJCC promulgates best staging practices through each new edition in an effort to provide cancer care providers with a powerful, knowledge-based resource for the battle against cancer. In this commentary, the authors highlight the overall organizational and structural changes as well as "what's new" in the Eighth Edition. It is hoped that this information will provide the reader with a better understanding of the rationale behind the aggregate proposed changes and the exciting developments in the upcoming edition. **CA Cancer J Clin 2017;67:93–99. © 2017 American Cancer Society.**

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Introduction and Overarching Vision of AJCC Staging

The Eighth Edition of the *AJCC Cancer Staging Manual*, published in October 2016, is a compendium of all currently available information on the staging of adult cancers for all clinically important anatomic sites. It builds on a rich historical legacy of dynamic vision, international synergy, and the robust principles of cancer classification using the anatomic extent of disease tumor, lymph node, metastasis (TNM) concept first developed by Pierre Denoix in the 1940s and 1950s.[1] The First Edition of the *AJCC Cancer Staging Manual* was published in 1977 and broadened the scope of the American Joint Committee on Cancer (AJCC) in the staging of cancer for American physicians and registrars. The founding editors adroitly noted that: "*Staging of cancer is not an exact science. As new information becomes available about etiology and various methods of diagnosis and treatment, the classification and staging of cancer will change. Periodically, this manual*

will be revised so that it reflects the changing state of the art. However, changes will occur only at reasonable periods."[2] The Second Edition of the manual (1983) included updates and staging of additional sites. That edition conformed to the staging proposed by the TNM Committee of the International Union Against Cancer (UICC).[3] The editors of the Second Edition made an astute comment that is very appropriate today: *"At the present time, the anatomic extent of the cancer is the primary basis for staging; the degree of differentiation of the tumor and the age of the patient are also factors in some cases. In the future, biologic markers and other factors may also play a part."* The Third, Fourth, and Fifth Editions of the *AJCC Cancer Staging Manual* were published in 1988, 1992, and 1997, respectivelly.[4-6] In the United States during the 1990s, the importance of AJCC cancer staging was heightened by the mandatory requirement that Commission on Cancer-accredited hospitals use the AJCC TNM system for cancer reporting, which prompted the education of all physicians and registrars in its use. In 2002, the Sixth Edition judiciously added a select few nonanatomic factors that modified stage groups to recognize the emerging importance of these nonanatomic factors as complementary to staging approaches.[7] In the Seventh Edition, published in 2009, more relevant nonanatomic markers were expanded to further define stage groups and to make staging more efficient for prognostication and to guide therapy.[8] The heading "Anatomic Stage and Prognostic Groups" used in the Seventh Edition replaced the previously used "Anatomic Stage" to designate this slightly modified approach to determining cancer stage based on stage grouping tables. The Eighth Edition, while maintaining the anatomic extent of disease as its foundation, makes a further tangible effort to transition from the more traditional "population-based" approach by incorporating biologic and molecular markers to create a more contemporary "personalized approach," one that is not only relevant as a robust classification system for population-based analyses but is equally powerful in determining therapy at an individualized level at the bedside. Consequently, the term "prognostic stage groups" is now promoted in the Eighth Edition to merge the 2 concepts (anatomic stage and prognostic groups) in tables that are used to determine the stage group for a particular cancer.[9] Detailed prognostic factor discussions are provided for each cancer in distinct sections to provide a more global landscape of the current clinically relevant cancer signature beyond that of stage alone.

The AJCC promulgates best staging practices through each new edition in an effort to provide cancer care providers with a powerful, knowledge-based resource for the battle against cancer. It also strives to maintain its role in education, advocacy, and promotion of the system within the cancer care community—physicians (including medical students and residents), tumor registrars, statisticians, public health policy makers, and patients. In partnership with our founding member, the American Cancer Society, we take this opportunity to inform the broad cancer community of several important developments in the new Eighth Edition. Over the next 12 months, select articles will be published in this journal that will focus on site-specific seminal developments, providing updates and highlighting the changes and the justification behind changes. These sites include lung, head and neck, prostate, breast, melanoma, and esophagus.

New Features in the Eighth Edition:

Organization of the AJCC Eighth Edition Team

In contrast to prior editions, a much larger editorial board with an editor-in-chief and wide representation of multidisciplinary groups of specialists, from surgical oncology, radiation oncology, medical oncology, anatomic and molecular pathology, imaging, biostatistics, population sciences, the registrar community, and key administrative staff, was created. Seven AJCC Cores, with defined functions and expertise, were introduced: Precision Medicine Core, Evidence Based Medicine and Statistics Core, Imaging Core, Content Harmonization Core, Data Collection Core, Professional Organization and Corporate Relationship Core, and Administrative Core. Disease sites, each typically containing several anatomically related cancers, were reorganized into 18 expert panels. In all, approximately 420 contributors from 181 institutions, 22 countries, and 6 continents participated in the massive and coordinated effort to produce the Eighth Edition.

Organization of AJCC Eighth Edition Content

The new *AJCC Cancer Staging Manual* provides several key introductory chapters and is then organized primarily by groups of similar cancer types or disease sites (eg, thorax, female reproductive organs, endocrine system, etc). Each chapter includes a discussion of information relevant to staging the cancer type, the data supporting the staging, and the specific rationale for changes in staging. In addition, it includes definitions of seminal prognostic factors, including those required for stage grouping, those recommended for clinical care, and those recommended for collection in cancer registries. Each chapter ends with the specific definitions of T, N, and M categories; prognostic stage groups; and anatomic stage groups.

General Staging Rules Revisited and Content Harmonization Across the Cancer Staging Continuum

The Content Harmonization Core was charged with the task of comprehensively analyzing staging nomenclature for

TABLE 1. AJCC on Cancer Levels of Evidence[a]

1. The available evidence includes consistent results from multiple large, well-designed, and well-conducted national and international studies in appropriate patient populations, with appropriate endpoints and appropriate treatments. Both prospective studies and retrospective population-based registry studies are acceptable; studies should be evaluated based on methodology rather than chronology.
2. The available evidence is obtained from at least one large, well-designed, and well-conducted study in appropriate patient populations with appropriate endpoints and with external validation.
3. The available evidence is somewhat problematic because of one or more factors, such as the number, size, or quality of individual studies; inconsistency of results across individual studies; appropriateness of the patient population used in one or more studies; or the appropriateness of outcomes used in one or more studies.
4. The available evidence is insufficient because appropriate studies have not yet been performed.

Abbreviation: AJCC, American Joint Committee on Cancer.
[a]Reproduced from Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017.

accuracy and consistency, minimizing legacy version ambiguities, and presenting a detailed analysis and overall update of the general staging rules that can be applied across all disease sites and along the cancer staging continuum—including clinical, pathological, posttherapy/post-neoadjuvant therapy, recurrence/retreatment, and autopsy classifications. It is well established that staging requires the collaborative effort of many professionals, including the managing physician, pathologist, radiologist, and others. While the pathologist, radiologist, and other health care providers generate important staging information and may contribute important T-related, N-related, and/or M-related information, stage is ultimately defined from the synthesis of an array of patient history and physical examination findings supplemented by imaging and pathology data. Only the treating physician (or the managing physician[s] with complete access to the full set of patient information) can assign the patient's stage, because only (s)he routinely has access to all of the pertinent information from physical examinations, imaging studies, biopsies, diagnostic procedures, surgical findings, and pathology reports. It is critical that this information is accurately recorded in the patient record to enable the synthesis of the relevant factors into a prognostic stage group.

Centralizing AJCC Staging Content Electronically

For the first time, the AJCC will deliver *AJCC Cancer Staging Manual* content by using additional methods and tools to improve ease of maintenance of content and easier access and use while at the same time ensuring consistency and accuracy of content. All staging content is centrally maintained and curated in a Component Content Management System and is distributed electronically through the AJCC's Application Programing Interface (API). Ensuring the highest fidelity and accuracy of the AJCC staging content, electronic health record, cancer registry software vendors, and electronic application developers will benefit from this digitally structured content, which facilitates its programmatic incorporation directly into their products through licensed access to the API. All components of the *AJCC Cancer Staging Manual* will be accessible through the API—the most significant of which are the T, N, and M categories and criteria; the definitions of prognostic factors required for staging; and the prognostic stage groups. Software developers will benefit from this electronic delivery method, as it reduces the amount of time required to integrate AJCC cancer staging content into software and clinical workflows for use at the point of patient care.

Presentation of Levels of Evidence for Changes to Staging

The Evidence Based Medicine and Statistics Core established the levels of evidence to guide current and future changes to AJCC staging content (Table 1).[9] The evidence level is provided along with any change to a disease site staging system. These levels provide transparency for the expert panel decisions and help establish a baseline for measuring how the evidence evolves over future editions of the AJCC TNM staging system. Levels of evidence are applied to changes in AJCC TNM classification as well as to the prognostic factors included in prognostic stage groups and recommended for clinical care. No changes to stage definition were made on level IV evidence.

Imaging in Cancer

An active Imaging Core has made seminal and consistent contributions to all expert panels, and for the first time the staging manual now includes disease site-specific information about the most appropriate imaging evaluation in each disease site. The Imaging section in each chapter typically describes which imaging tests are most appropriate for assessing tumor stage information (ie, tumor size, nodal involvement, metastases) for the cancer; the temporal order in which the appropriate imaging tests are typically performed; and the specific T, N, and M information that can be extracted from imaging tests for the cancer.

Where appropriate, specific issues, pitfalls, cautions, and reminders for interpreting imaging stage information for the cancer are also included, as well as links or references to disease-specific or specialty-specific society guidelines. Standardized reporting of imaging reports pertaining to cancer is promoted.

Prognostic Factors in Cancer: Toward a More Individualized Approach

The Cancer Genome Atlas project, the International Genomic Consortium, and other comprehensive scientific endeavors have allowed us to better understand the molecular underpinnings of cancer in terms of oncogenesis, progression, and resistance. The concept of molecular classification of cancer at a clinically relevant level is now accepted as an imminent reality. It is widely believed that the new molecular classification schema will complement traditional and time-honored classifications, such as anatomic staging, histological typing, and grading. These advances provide a transformational opportunity to positively impact cancer management. As new technologies catapult prognostic and predictive factor assessment in cancer, the continued discovery of additional clinically relevant markers makes it necessary to include them judiciously in staging algorithms and will likely require the development of novel strategies beyond those currently adopted. In the Eighth Edition, the AJCC has expanded the use of nonanatomic prognostic factors and biomarkers in assigning prognostic stage groups. The AJCC will continue to place an emphasis on changes and developments that lead to improved clinical decision making and/or improved predictive accuracy in stratifying patients. The Prognostic Factors section of each disease chapter describes factors that affect patient prognosis. These are consistently presented in the following format across all chapters.

The Prognostic Factors Required for Stage Grouping section describes factors that strongly correlate with prognosis and are included as categories used to determine stage group in the prognostic stage table. Levels of evidence are provided. Because staging is applicable universally, including under-resourced nations where not all prognostic factors may be obtainable because of limited resources, for every cancer type in which prognostic factors are incorporated into staging, a stage group based solely on anatomic information can still be generated, even if prognostic factors are not available. More information regarding how to stage when prognostic factors are not available is outlined in Chapter 1 of the Eighth Edition, which discusses general staging rules in greater detail than in prior editions. Several rules have also been updated.

The Additional Prognostic Factors Recommended for Clinical Care section describes factors that are clinically significant but are not included in prognostic stage tables. Levels of evidence are provided. It is important to collect these factors in cancer registries and databases to measure their impact on prognosis; indeed, some of these factors are critical for future prognostic and predictive model building and for clinical tool development and validation. Examples include recording of carcinoembryonic antigen for colon cancer.

The Emerging Factors for Clinical Care section describes factors for which there is not yet sufficient evidence to support a recommendation for routine use. On the basis of institutional and national database priority, many of these variables are abstracted. It is hoped that, as the evidence base grows, the utility of these factors will be reexamined. Because of the evolving nature of this information, emerging factors are not included in the print manual but will be made available—with a plan for regular periodic updates—on the AJCC Web site (cancerstaging.org).

Risk-assessment models for several cancers are increasingly being published and are often used in clinical practice. The AJCC Precision Medicine Core developed quality and consistency guidelines for potential AJCC endorsement of validated and published clinical tools that include rigorous exclusion and inclusion criteria to be applied to the assessment of existing and future risk-assessment models.[10] A section on currently available risk assessment models is included in the Disease Site chapter for a few pilot sites in the Eighth Edition, including lung, prostate, melanoma, breast, and colorectal cancers. The review and development of prognostication modeling tools will be an ongoing effort within the AJCC, and meritorious tools appropriate for AJCC endorsement will be added as this work progresses. To foster transparency, prognostication tools reviewed for the Eighth Edition and the details of the process of adjudication for AJCC endorsement will be made available on the AJCC Web site.

Factors for Recommendations for Clinical Trial Stratification will also be available on the AJCC website. The goal of this section is to guide organizations that design clinical trials with regard to the most important prognostic factors of a given cancer that should be built into the eligibility and/or stratification criteria for a clinical trial. The objective of the AJCC is to fully support clinical trial development by specifically identifying these factors, and the AJCC plans to periodically review these site-specific factors to continue to inform contemporary clinical trial design.

A True International Effort to Derive TNM Staging and for a Common Language of Cancer

On the basis of a joint agreement since the 1980s, the collaboration between the AJCC and UICC has resulted in concordant stage definitions and simultaneous publication of the *AJCC Cancer Staging Manual* and the *TNM*

TABLE 2. Summary of What's New in the Eighth Edition AJCC Cancer Staging Manual[a]

Revised organizational structure

- Eighteen expert panels and 7 cores (420 contributors from 181 institutions, 22 countries and 6 continents)
- Cores: Precision Medicine, Evidenced Based Medicine and Statistics, Imaging, Content Harmonization, Professional Organization and Corporate Relationship, Data Collection, Administrative
- Expanded Editorial Board with Editor-in-Chief

Updates

- General staging rules (Chapter 1)
- Staging systems in several chapters
- Histologic classifications and grading systems
- WHO/IARC histology codes
- More illustrations

New paradigms

- HPV (Oropharyngeal carcinoma staging systems based on HPV status)
- Separate staging systems for patients with neoadjuvant therapy (Esophagus and stomach)
- Bone and soft tissue sarcoma (Separate staging systems based on anatomic sites)

New features

- Levels of evidence provided when revisions to staging systems are made
- Imaging section
- Risk assessment models for select cancer sites
- Recommendations for clinical trial stratification (Web only)
- Prognostic factors
  - Required for prognostic stage grouping
  - Recommended for clinical care
  - Emerging factors (Web only)

New chapters/staging systems

- Risk Models for Individualized Prognosis in the Practice of Precision Oncology
- Cervical Nodes and Unknown Primary Tumors of the Head and Neck
- HPV-Mediated (p16+) Oropharyngeal Cancer
- Cutaneous Squamous Cell Carcinoma of the Head and Neck
- Thymus
- Bone: Appendicular Skeleton/Trunk/Skull/Face, Pelvis, and Spine
- Soft Tissue Sarcoma of the Head and Neck
- Soft Tissue Sarcoma of the Trunk and Extremities
- Soft Tissue Sarcoma of the Abdomen and Thoracic Visceral Organs
- Soft Tissue Sarcoma of the Retroperitoneum
- Soft Tissue Sarcoma–Unusual Histologies and Sites
- Parathyroid
- Leukemia

Split chapters

- Oropharynx and Hypopharynx (p16−) (Previously pharynx)
- Nasopharynx (Previously pharynx)
- Pancreas–Exocrine (Previously endocrine/exocrine pancreas)
- Neuroendocrine Tumors of the Pancreas (Previously endocrine/exocrine pancreas)
- Neuroendocrine Tumors of the Stomach
- Neuroendocrine Tumors of the Duodenum and Ampulla of Vater

- Neuroendocrine Tumors of the Jejunum and Ileum
- Neuroendocrine Tumors of the Appendix
- Neuroendocrine Tumors of the Colon and Rectum
- Thyroid–Differentiated and Anaplastic
- Thyroid–Medullary
- Adrenal Cortical Carcinoma
- Adrenal–Neuroendocrine

Merged chapters

- Ovary, Fallopian Tube, and Primary Peritoneal Carcinoma

Deleted chapters

- Cutaneous Squamous Cell Carcinoma and Other Cutaneous Carcinomas for All Topographies
  - Specific System Devised for Cutaneous Carcinomas Arising in Head and Neck Sites

Future planned updates at www.cancerstaging.org

- Eighth Edition content will be available to electronic health record vendors, registry software vendors, and other users through an Application Programming Interface (API)
- Cancer staging forms will be made available
- Rolling updates
  - Emerging Factors for Clinical Care
  - Recommendations for Clinical Trial Stratification
  - Refined Risk Assessment Models for Current Cancers Sites
  - Development of Risk Assessment Models for Additional Cancer Sites

Abbreviations: AJCC, American Joint Committee on Cancer; HPV, human papillomavirus; IARC, International Agency for Research on Cancer; prev., previously; WHO; World Health Organization.
[a]Reproduced from Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017.

Classification of Malignant Tumors by the UICC.[11] To build on this partnership, during the development of the Eighth Edition of the AJCC system, UICC members were proactively represented on the editorial board and on all expert panels. This has enabled greater synergy between the TNM stage definitions promulgated by the respective 8 editions. International participation was also assimilated by the invitation of select international experts to serve on different expert panels. International consortia and data from groups, such as an international collaborative that is collecting outcome and staging data in melanoma and gastric cancer, the International Association for the Study of Lung Cancer, the Worldwide Esophageal Cancer Collaborative, and the Eye Cancer Network's Universal Eye Cancer Database Project, have greatly enriched the Eighth Edition content.

Summary of Changes

As is hopefully evident from this overview, a herculean effort has been undertaken to update and improve staging for the Eighth Edition *AJCC Cancer Staging Manual*. This task has been performed by a team overwhelmingly made up of volunteers who are committed and passionate to impact cancer care and outcomes. Table 2 provides a summary of many of the new features, new and/or reorganized chapters, as well as an overview of new staging paradigms.[9]

The work of the Eighth Edition is not yet entirely over. An additional herculean effort is underway to incorporate new cancer staging rules into electronic health records so that this information can be captured at the point of care, and into cancer registry software so that it can be accurately collected for surveillance and research. While AJCC has primed the content for faster electronic integration by developing the API, software developers need time to build the infrastructure to receive that information. After much discussion with our partners at the National Cancer Institute (NCI-SEER), Centers for Disease Control and Prevention National Program of Cancer Registries (CDC-NPCR), the College of American Pathologists (CAP), the National Comprehensive Cancer Network (NCCN), the National Cancer Data Base (NCDB), and the Commission on Cancer (CoC), the AJCC Executive Committee made the decision to delay the implementation of the Eighth Edition Cancer Staging System to January 1, 2018. In the interim, clinicians should continue to use the latest information for patient care, including scientific content of the

Eighth Edition Manual. From the documentation perspective, all newly diagnosed cases through December 31, 2017, should be staged with the Seventh Edition. The time extension will allow all cancer staging stakeholders who utilize AJCC staging content to develop and update protocols and guidelines, and for software vendors to develop, test, and deploy their products in time for the data collection and implementation of the Eighth Edition in 2018.

Conclusion

The expanded, revised, and updated Eighth Edition of the *AJCC Cancer Staging Manual*, along with its new and exciting electronic and print product capabilities and the series of articles in this journal over the next 12 months, will be a powerful resource for patients and physicians alike. Refining standards for the best possible staging system is an ever-evolving process. The journey bridging the population and the individualized approach is designed to pave the foundation for continued relevancy of cancer staging as we make further strides in this era of precision molecular oncology. ■

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