New protocols on deck as pathology helps reshape cancer staging

Anne Paxton

December 2016—It's a familiar campus lament. New editions of textbooks in some academic fields have become notorious for providing little more than a few extra paragraphs of text or a few more references and altered pagination—mainly, students suspect, to serve as a damper on the textbook resale market. What is happening with a key text in the field of cancer care, however, is in marked contrast. The changes contained in the 8th edition of the *AJCC Cancer Staging Manual* of the American Joint Committee on Cancer, slated to take effect Jan. 1, 2018, are the opposite of cosmetic.

This first revision of the staging manual in seven years presents a major expansion and reconfiguring of cancer staging classifications, a transformational shift of approach to accommodate molecular advancements, and detailed added discussion of prognostic factors. The 8th edition not only sets a high-water mark for international cooperation but also represents a milestone for pathology. This is the first time that a pathologist, rather than a surgical oncologist, has been selected as editor-in-chief to lead the revisions, and at least one pathologist was assigned to assist on each chapter.

Dr. Baker

The 8th edition is one of the most significant sets of changes in the staging manual's history, says Thomas P. Baker, MD, chair of the CAP Cancer Committee. "It's a pretty comprehensive overhaul that affects every single tumor that is staged." Mary K. Washington, MD, PhD, a past CAP Cancer Committee chair who served on the AJCC editorial board for the 8th edition, agrees the new edition is very different from the 7th. "Many more of the non-anatomic factors are incorporated into the prognostic staging systems, staging definitions are changed or new for many sites, and there's finally a systematic attempt to go beyond the tumor-node-metastasis system to make it more relevant to personalized medicine."

Since cancer staging is at the core of the CAP's cancer protocols, the new staging manual will mean changing every CAP cancer protocol as well, Dr. Baker adds. "We have 66 protocols that we're currently updating and they will be available on paper, but they also need to be converted into electronic form for the electronic checklist. Then the vendors who use the electronic checklist need to put the changes into their LISs."

The protocols as well as the inspection process will be adapted to match the changes. Revised protocols will be released in the second quarter of 2017, well in advance of their effective date. This will give all stakeholders time to make the adjustment to the new staging and new protocols. Although the 8th edition was initially announced and distributed in September 2016 for a Jan. 1, 2017 effective date, by mid-November the AJCC decided to defer the effective date to Jan. 1, 2018—largely to allow software vendors and laboratories time to adapt their LIS worksheets and cancer reporting systems to the modifications.

"The time extension will allow all partners 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 8th edition in 2018," the AJCC executive committee announced. The decision to delay was made in collaboration with

the CAP; the National Cancer Database; the Centers for Disease Control and Prevention; the National Comprehensive Cancer Network; the National Cancer Institute's Surveillance, Epidemiology, and End Results program; and the American College of Surgeons' Commission on Cancer.

Many questions surround the implementation process, and it may appear that clinicians and pathologists will need bifocals to grapple with the transition year, because the clinical side of cancer patient care is going to be operating on a somewhat different track than the data reporting side. But that split is often a familiar state of affairs anyway in cancer care, as practice guidelines, electronic data management, and data collection are never in perfect synchrony, according to CAP officials who have been involved in the cancer staging and protocols efforts.

Michael A. Berman, MD, chair of the CAP Pathology Electronic Reporting Committee, suggests that this transition period is not different from those in the past. "The issue we are all facing is in dealing with cancer patients and staging systems, cell types, personalized medicine, and companion diagnostics: This is a really fast-moving target." The challenge, he says, is getting the most up-to-date information into the hands of the treating physicians and tumor registries to improve patient outcome. "All stakeholders need to work together to make the transition as seamless and efficient as possible," he adds.

In terms of the impact the new staging manual will have on pathology practice, the most important facts are as follows:

- The AJCC 8th edition staging manual has been published, but clinicians and pathologists will continue to use the 7th edition to stage all new cancer patients and to produce pathology reports throughout 2017.
- For patient care, clinicians can use the scientific content of the 8th edition immediately. Pathologists can immediately rely on the new scientific content in reporting on whatever they see in their specimens.
- In the second quarter of 2017, new CAP cancer protocols will be released, with a note that the implementation date will be Jan. 1, 2018.
- Laboratories will not be surveyed for patient reports using the AJCC 8th edition until after Jan. 1, 2018, the official release of the revised CAP cancer protocols.

Staging is the nomenclature and the global common language of cancer, says Mahul Amin, MD, former chair of the CAP Cancer Committee and the AJCC editor-in-chief who led the development of the 8th edition. "It's a fundamental language, and with each new edition of the staging manual, it is becoming the standard of classifying cancer across the globe."

Dr. Amin

Development of the 8th edition was a multidisciplinary effort of more than 430 surgical and medical oncologists, pathologists, radiologists, and public health experts from 184 institutions in 22 countries and six continents. Compared with prior editions, Dr. Amin says, this effort had exceptional international cooperation, almost double that of prior editions.

Dr. Amin, who will take a position in January as the Gerwin endowed chair of the Department of Pathology and Laboratory Medicine at the University of Tennessee Health Sciences Center in Memphis, has assisted and led the development of reporting and staging standards for 20 years, first in his role as CAP Cancer Committee chair, during which time the CAP cancer protocols were mandated as part of the American College of Surgeons accreditation program, and more recently as editor-in-chief of the 8th edition.

Generally, there is a seven-year gap between updates of the staging system, Dr. Amin says, noting that work on the 8th edition began in 2013. But in 40 years and seven prior editions, surgical oncologists have primarily led the updates. “It is a privilege for the pathology community to have an individual from their discipline lead worldwide cancer staging efforts,” he says.

One of the most important features of the 8th edition is essentially a shift in mission, he notes. The new manual is meant to serve as a bridge between a traditional population-based approach to cancer staging and a more personalized or individualized approach. Traditionally, cancer has been classified based primarily on the AJCC’s TNM system—anatomic tumor size, nodal involvement, and metastatic disease—which has been in place since the first staging manual was published in 1977.

Since the 7th edition of the staging manual was published in 2009, medical science has established that genomic alterations drive cancer and that these may vary considerably even among tumors that appear to be identical under the microscope and thus in the same category. “The concept of molecular classification of cancer at a clinically relevant level is now accepted as an imminent reality,” Dr. Amin says. “Given the massive influence of clinical, molecular, and histologic factors in select cancers that are beyond extent of disease, it was essential to take a more comprehensive approach.” Through the introduction of “prognostic stage groups” in the various cancers, the staging manual team has incorporated new, relevant non-anatomic factors to refine the traditional concepts of cancer staging.

International variances will remain, since the manual is used throughout the world, including in many geographic regions where biomarker information is not available. In such cases, the AJCC says, “anatomic stage” will continue to be used. But in developed countries where biomarkers are routinely used and available, physicians and registrars will be expected to use prognostic stage groups.

The 8th edition features other important changes. For a number of organ sites, the evidence-based revisions for staging cancer can include the ration-ale and rules for staging, the definitions of TNM, stage groupings, and histologic grade. “There are new chapters, some chapters previously grouped are now split, some are deleted, and some are merged. There’s been a massive reorganization,” Dr. Amin says.

In addition to revisions to existing staged cancers—for example, ovary, fallopian tube, and primary peritoneal carcinoma have been merged into one chapter, while lobular carcinoma in situ was eliminated as a breast cancer diagnosis—12 new staging systems have been introduced: cervical nodes and unknown primary tumors of the head and neck; oropharynx, HPV-mediated (p16+); 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; and leukemia.

Three new paradigms are included as well: HPV (oropharyngeal carcinoma staging systems based on HPV status); separate staging systems for patients with neoadjuvant therapy (esophagus and stomach); and the inclusion of the

H category to TNM—TNMH—in retinoblastoma, to include the powerful impact of hereditary cancer in the prognosis of these tumors.

The 8th edition promotes the term prognostic stage groups to merge the two concepts of anatomic stage and prognostic groups, in the tables that are used to determine the stage group for a particular cancer, to make staging more relevant at the individualized patient level, Dr. Amin says. For each cancer, there are detailed prognostic factor discussions that "expand the clinically relevant cancer signature beyond that of stage alone." The prognostic factors are described from three standpoints: prognostic factors required for stage grouping, those required for clinical care, and emerging prognostic factors. It's important for pathologists to be aware of all three since they have different ramifications, he says.

Among the manual's other new features are indications of the level of evidence when revisions to staging systems are made, risk-assessment models for select cancer sites, and recommendations for clinical trial stratification.

Imaging is featured more prominently. For the first time, information about the most appropriate imaging evaluation for each disease site is included—for example, which imaging tests are most appropriate for assessing tumor stage information for the cancer, the order in which the tests are typically performed, and specific T, N, and M information that can be extracted from the imaging tests.

The AJCC editorial board took a novel approach in organizing seven AJCC "cores" or groups of contributors with defined functions and expertise. These included cores for precision medicine, evidence-based medicine and statistics, imaging, content harmonization, data collection, professional organization and corporate relationship, and administrative. Eighteen expert panels were appointed to focus on disease sites (e.g., thorax, female reproductive organs, endocrine system), each typically containing anatomically related cancers.

Also new with this edition is digitally structured staging content, available in addition to the traditional printed manuals. A component content management system will distribute content electronically through the AJCC's application programming interface, or API, to which software vendors may obtain access by license.

Many 8th edition changes were made at the suggestion of other pathologists, says Dr. Washington, of Vanderbilt University Medical Center. "The introduction and the first chapter of the manual, called 'Principles of Cancer Staging,' have been rewritten to address a number of ambiguities and make several clarifications. The rest of us had responsibilities for specific sections."

Among her assignments were the hepatobiliary chapters, as well as colorectal cancer and carcinoma of the appendix. While the colorectal cancer chapter saw only clarifications of ambiguous language, pathologists suggested and led changes in the T-category definitions and the pancreas exocrine staging system. "We added new T-category definitions for low-grade mucinous neoplasms of the appendix, which previously most pathologists didn't stage, so this expands the number of lesions pathologists will be dealing with."

Dr. Washington

Carolyn Compton, MD, PhD, a past chair of the CAP Cancer Committee and of the AJCC, led the AJCC precision medicine core, Dr. Washington says. "They evaluated a number of prognostic systems that had been published in the literature to see how applicable they were. Several chapters have risk-assessment models, including the colorectal chapter, which basically gives a review of the models they looked at. And they listed three approved

prognostic tools for colorectal cancer that were considered useful."

According to the AJCC, after reviewing hundreds of publications, the breast expert panel decided to include estrogen receptor and progesterone receptor status, HER2 status, and grade in the creation of a prognostic stage, combined with the traditional TNM variables of anatomic stage. For patients with T1-2N0M0, ER-positive, HER2-negative tumors, information from multigene panels was also incorporated.

Use of these prognostic tools is not necessarily the current standard of care, Dr. Washington cautions. "They're very dependent on the type of cancer, and you have to be careful about applying them. But this gives us a framework for developing really good tools that will be the standard of care."

Although the 8th edition contains many clarifications about what data should be collected and when and how to use it, data collection was one of the main drivers of the decision to delay implementation. Worldwide, the traditional TNM system for breast cancer, for example, will remain much as it is. "But in the U.S., they are asking people to use a prognostic stage grouping that incorporates things like HER2, and it's considerably more complicated," Dr. Washington explains. "What happened was that CDC and NCI-SEER ran a test to see if they had the data fields to adequately capture the data. And it turns out they actually did not."

"It's a big deal for them," she notes, particularly because the CDC and NCI-SEER are the agencies that will train tumor registrars in the changes. "Basically when they did this test, it turned out that more than 40 percent of patients with stage I–III breast cancer were restaged—half higher, half lower," when compared with 7th edition criteria. This complexity added to the decision to delay implementation to ensure that the cancer care community has the necessary infrastructure for documenting 8th edition staging, the AJCC says.

Managing the CAP protocols for electronic reporting of data will be a key challenge as pathologists transition to 8th edition cancer staging standards, says Dr. Berman, of Jefferson Hospital, Jefferson Hills, Pa. The Pathology Electronic Reporting, or PERT, Committee that he chairs is composed of pathologists with various practice and informatics backgrounds, representatives from national American and Canadian tumor registry organizations, highly technologically trained CAP staff, and liaisons to other like-minded organizations such as the American Society of Clinical Oncology. The committee meets weekly to discuss how to best structure cancer-related data in the pathology report. The needs of the data enterer (i.e. input by the pathologist), the format of the output (the human readable report for use by the treating physician), and downstream advantages of discrete data collection are all taken into consideration.

Once the content experts from the CAP Cancer and Cancer Biomarker Reporting committees have created a cancer protocol, "PERT is in charge of converting that content into an electronic format." PERT also works closely with information system vendors on how that format can be implemented in the pathology report.

"Advantages of using electronic cancer checklists [eCC] include enhanced data interoperability and transportability, ensuring that appropriate parameters are consistently reported, and improved data-mining capabilities," Dr. Berman says.

The stage of the tumor is one of the parameters classically captured in a checklist or cancer protocol. "The pathologist is providing crucial data to assist tumor staging, but it is the medical oncologist or treating clinician who is responsible for defining the pTNM classification at the time of the definitive resection. Accordingly, these parameters are key to our dataset," he says. It is time-consuming to align the duties of the cancer protocol review teams, PERT, and the LIS vendors while maintaining strict quality control and assurance of the cancer protocols and eCCs, including the ability for public comment. "For this reason, the delay in implementation by the AJCC is welcomed. Going forward, it is planned that with improved technology, the process of revising CAP cancer protocols and eCCs will be streamlined, lessening some of the angst elicited by the current situation."

Given the lengthy process of developing the 8th edition, there has been discussion of adopting a "rolling release" process to respond to the "fast moving target" nature of cancer care. "That would allow changes in one chapter in

the manual rather than waiting for a full manual revision," Dr. Berman says. Other entities already use rolling releases for their updates, such as the World Health Organization for its WHO Classification of Tumours series.

The AJCC has indicated that data inaccuracies are likely to crop up during the transition, and Dr. Baker believes this could affect cancer surveillance at the tumor registries. Changes to the staging system will impact much of the staging information, so until the tumor registrars have updated their software, there will be several months in which data may not be accurate and will have to be changed later, says Dr. Baker, of The Joint Pathology Center, Defense Health Agency National Capital Region Medical Directorate, Bethesda, Md.

However, for the data collection that must be conducted by the tumor registrars, switches from one edition to the next need to be clear, says Doug Murphy, CAP senior technical analyst. "Staging hasn't changed in a long time. When we do these sort of system changes, they're kind of quantum leaps." While this system change takes place in 2018, "treatment decisions may change earlier based on some of the elements of the 8th edition, in the same way that oncologists and clinicians traditionally alter their treatments based on new information." But for data collection, "you really need these firm cutoff dates to avoid having muddy data."

For clinical care, the interim mandate from the AJCC means both editions will be used. The AJCC is requiring that all newly diagnosed cases through Dec. 31, 2017 be staged with the 7th edition, but said in a statement that "clinicians will use the latest information for patient care, including scientific content of the 8th edition manual."

Some experts don't see this as a problem. If an oncologist sees a biopsy staged under the 7th edition (as required in 2017), "that doesn't mean they're going to use antiquated information to treat that patient," Dr. Baker points out. "What they will do is compare the information with the 8th edition to see whether the staging would be the same or needs to be upstaged to a different stage."

One solution, Dr. Washington says, will be for pathologists to enhance their 7th edition staging with comments referring to the 8th edition staging—for example, by noting that "AJCC 8th edition staging is T3N1" or something similar. "I think there may be some confusion during the transition year, yes. It will be important for pathologists to be very explicit and clear in their reports and make liberal use of comments to explain." The CAP plans to provide guidance on its website to help pathologists with the changeover, she says.

As these many intricacies indicate, the whole staging process and the roles pathologists have in disseminating staging have changed considerably with the 8th edition, Dr. Amin says. But there is an upside. "With this edition, the incorporation of molecular diagnostics and other non-anatomic pathologic factors, as appropriate, further empowers pathologists and their role in contemporary multidisciplinary cancer care." The changes are complex, but he believes that the CAP cancer protocols, when released next year, will help pathologists make the adjustment.

"Such a massive change cannot be done at the flip of a switch, but in the past it's been more tumultuous than now," Dr. Amin says. "When I was chair of the CAP Cancer Committee, we took an important step in making sure each member of that committee was involved with the formulation of AJCC staging. Then, once the content was ready, the AJCC licensed the College to use it in order to revise the CAP cancer protocols."

Fortunately, thoughtful communication between the AJCC and the CAP has smoothed the way, and the CAP members who were involved with staging changes in the 8th edition have been able to return to the CAP cancer protocols and revise them, update the checklist, and update the protocols in the electronic systems.

"The 8th edition is almost twice the size in content and contains five times more illustrations than the preceding version and provides multidisciplinary content useful for pathologists to understand," Dr. Amin says. Despite all the changes, "the pathology community does not need to worry."

"The cancer protocols will give the end users what they, as pathologists, will minimally need to provide in their

reports to guide further cancer management.”
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